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(71) Applicant (for all designated States except US): MIL-  
LENNIUM PHARMACEUTICALS, INC. [US/US]; 40  
Landsdowne Street, Cambridge, MA 02139 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): POWELL, Douglas,  
M. [US/US]; 62 Grist Mill Road, Littleton, MA 01460  
(US).

(74) Agent: SIOUSSAT, Tracy, M.; Millennium Pharmaceuti-  
cals, INC., 40 Landsdowne Street, Cambridge, MA 02139  
(US).

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(54) Title: METHODS AND COMPOSITIONS FOR TREATING AIDS AND HIV-RELATED DISORDERS USING 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982, OR 46777

(57) Abstract: The present invention relates to methods for the diagnosis and treatment of AIDS or an HIV-related disorder or disorders. Specifically, the present invention identifies the differential expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982, and 46777 genes in tissues relating to AIDS or an HIV-related disorder, relative to their expression in normal, or non-AIDS or HIV-related disease states, and/or in response to manipulations relevant to AIDS or an HIV-related disorder. The present invention describes methods for the diagnostic evaluation and prognosis of various HIV-related disorders, and for the identification of subjects exhibiting a predisposition to such conditions. The invention also provides methods for identifying a compound capable of modulating AIDS or an HIV-related disorder or disorders. The present invention also provides methods for the identification and therapeutic use of compounds as treatments of AIDS or an HIV-related disorder.

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**METHODS AND COMPOSITIONS FOR TREATING AIDS AND HIV-RELATED  
DISORDERS USING 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560,  
7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748,  
47161, 81982 OR 46777**

**Related Applications**

[0001] The present application claims the benefit of U.S. Provisional Application Serial No. 60/454,202, filed on March 12, 2003, of U.S. Provisional Application Serial No. 60/456,326, filed on March 20, 2003, of U.S. Provisional Application Serial No. 60/465,240, filed on April 24, 2003, of U.S. Provisional Application Serial No. 60/475,233, filed on June 2, 2003, of U.S. Provisional Application Serial No. 60/478,952, filed on June 16, 2003, of U.S. Provisional Application Serial No. 60/487,836, filed on July 16, 2003, and of U.S. Provisional Application Serial No. 60/500,111, filed on September 4, 2003. The entire contents of these provisional patent applications are hereby incorporated in their entirety by this reference.

**Background of the Invention**

[0002] Human Immunodeficiency Virus (HIV) is a member the lentivirus genus of the *Retroviridae* family. On the basis of serologic properties and sequence analysis of molecularly cloned genomes human lentivirus isolates are designated HIV-1 and HIV-2. A classification scheme based on the sequence of the viral envelope (env) protein recognizes several subtypes/clades (e.g. HIV-1 A-I). Viral diversification is a key feature of HIV phylogeny. Each subtype displays a high degree of variability. Mutations introduced by the error-prone viral reverse transcriptase represent the major factor for variation, but also recombination occurs within individuals infected with different clades. Molecular epidemiology studies indicate, that viral migration/trafficking rather than viral mutation is the ecologic driving force for the pattern of global variation and distribution.

[0003] HIV represents an enveloped virus with two identical copies of a (+)-stranded RNA genome of 9.2 kb in length coding for 9 structural and regulatory viral proteins. Initial steps of infection are mediated through specific interaction of the viral envelope glycoprotein and the major host cell receptor CD4 as well as specific coreceptors CXCR4 (T-troph)/CCR5 (M-troph). After penetration virion RNA is converted into double-stranded DNA by the viral reverse transcriptase. Concomitantly, viral integrase and host cell proteins carry out integration

of the linear DNA into the host cell genome to produce the provirus. This intracellular genomic form represents the template for synthesis of full length genomic or subgenomic (spliced and unspliced forms) single-stranded viral RNAs catalyzed by the cellular RNA polymerase II.

[0004] HIV encodes precursor polyproteins as well as additional open reading frames. The *gag*, *pol* and *env* genes encode precursors for the virion capsid proteins, several virion enzymes (protease, reverse transcriptase/RNase H, integrase) as well as the envelope glycoprotein, respectively. The transcriptional activator (*tat*) and regulator of viral transcription (*rev*) encode nonstructural essential proteins. In contrast *vif*, *vpr* (HIV-1), *vpu* (HIV-2) and *nef* encoded genes represent nonessential 'accessory' proteins, which are thought to exert their pleiotrophic regulatory/modulatory effects through specific interactions with several different host cell encoded proteins.

[0005] Based on an intimate host/virus relationship at each step the viral life cycle is susceptible to inhibiting host cell functions. A summary of examples (see section 4.2) will illustrate the mutual relation. With the exception of the lentiviruses productive infection of target cells by most retroviruses is dependent upon proliferation and concomitant nuclear membrane dissolution of the infected cell. Lentiviruses such as HIV can infect nonproliferating cell types such as macrophages and other terminally differentiated cells overcoming the need for cell division. Activated and resting CD4-positive T helper cells as well as macrophages represent the major target cells for HIV. The role of dendritic cells as well as glia cells in HIV propagation and (neuro)-pathogenesis is discussed controversially.

[0006] HIV has been shown to be the etiologic agent of the acquired immunodeficiency syndrome (AIDS). The virus is transmitted by exposure to body fluids of an infected person. Sexual transmission, blood transfusions as well as intravenous drug abuse comprise the major routes. Infection with HIV is characterized by relentless and progressive decline in both number and function of CD4-positive T helper lymphocytes, which play a central role in coordinating immune responses. Ultimately, the weakened immune system is unable to control and eradicate the virus, AIDS develops, which is often accompanied with other opportunistic infections. In the four decades that HIV has afflicted the human population virus spread led to the death of over 22 Million people. It is estimated that about 36 million people worldwide are infected with HIV.

[0007] Antiretroviral drug therapy mainly encompassing different combinations of nucleosidic, non-nucleosidic inhibitors of the viral reverse transcriptase as well as protease

inhibitors has dramatically improved the lives of those who receive drug treatment. However, current therapies only delay progression of illness and are unable to eradicate the virus. Moreover, drug resistance reappears as a significant problem, close to 50% of the patients fail to efficiently suppress viral replication on treatment mainly due to resistance issues and tolerability/compliance of current drug regimens. Thus, additional HIV therapies are urgently required.

### **Detailed Description of the Invention**

[0008] The present invention provides methods and compositions for the diagnosis and treatment of AIDS and HIV-related disorders.

[0009] "Treatment", as used herein, is defined as the application or administration of a therapeutic agent to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has a disease or disorder, a symptom of disease or disorder or a predisposition toward a disease or disorder, with the purpose of curing, healing, alleviating, relieving, altering, remedying, ameliorating, improving or affecting the disease or disorder, at least one symptom of disease or disorder or the predisposition toward a disease or disorder. A therapeutic agent includes, but is not limited to, small molecules, peptides, antibodies, ribozymes and antisense oligonucleotides. Representative molecules are described herein.

[0010] The present invention is based, at least in part, on the discovery that nucleic acid and protein molecules, (described infra), are differentially expressed in disease states relative to their expression in normal, or non- disease states. The modulators of the molecules of the present invention, identified according to the methods of the invention can be used to modulate (*e.g.*, inhibit, treat, or prevent) or diagnose a disease, including, but not limited to, AIDS and HIV-related disorders.

[0011] "Differential expression", as used herein, includes both quantitative as well as qualitative differences in the temporal and/or tissue expression pattern of a gene. Thus, a differentially expressed gene may have its expression activated or inactivated in normal versus disease conditions. The degree to which expression differs in normal versus disease or control versus experimental states need only be large enough to be visualized via standard characterization techniques, *e.g.*, quantitative PCR, Northern analysis, subtractive hybridization. The expression pattern of a differentially expressed gene may be used as part of a prognostic or diagnostic a disease, *e.g.*, AIDS and HIV-related disorders,



evaluation, or may be used in methods for identifying compounds useful for the treatment of a disease, *e.g.*, AIDS and HIV-related disorders. In addition, a differentially expressed gene involved in a disease may represent a target gene such that modulation of the level of target gene expression or of target gene product activity will act to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect a disease condition, *e.g.*, AIDS and HIV-related disorders. Compounds that modulate target gene expression or activity of the target gene product can be used in the treatment of a disease. Although the genes described herein may be differentially expressed with respect to a disease, and/or their products may interact with gene products important to a disease, the genes may also be involved in mechanisms important to additional disease cell processes.

[0012] An "AIDS- or HIV-related cell", as used herein, includes, but is not limited to, thymocytes, dendritic cells, T cells, macrophages, peripheral blood mononuclear cells (PBMC), lymphocytes, monocytes, leukocytes and lymphoid cells.

### **Molecules of the Present Invention**

#### **Gene ID 9145**

[0013] The human 9145 sequence, known also as 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD), is approximately 1348 nucleotides long including untranslated regions (SEQ ID NO:1). The coding sequence, located at about nucleic acid 102 to 980 of SEQ ID NO:1, encodes a 292 amino acid protein (SEQ ID NO:2).

[0014] As assessed by TaqMan analysis, 9145 mRNA expression was detected in thymocytes, dendritic cells, dendritic cell CD4+ T cell (DC/CD4) cocultures, T cells and macrophages. 9145 mRNA expression was highly induced by HIV infection in dendritic cells, DC/CD4, macrophages and thymocytes, and CD4+ T cells.

[0015] 9145 catalyzes the conversion of inactive cortisone to the active glucocorticoid cortisol. The principal glucocorticoid is cortisol. Cortisol is known to have a number of immunosuppressive effects including inhibition of mediators of inflammation, such as cytokines and prostaglandins. Cortisol inhibits production of IL-1 and IL-6 from macrophages and the production of inflammatory effects of bradykinin, platelet-activating factor and serotonin. Cortisol levels are elevated in HIV infected individuals which are correlated with disease progression. HIV patients have been demonstrated to have increased sensitivity to glucocorticoids due to enhanced receptor expression (*The Journal*

of Immunology, 2002, 169: 6361-6368). 9145 mRNA expression is primarily restricted to T cells, dendritic cells, macrophages and liver which contain large numbers of monocyte derived Kupfer cells. 9145 is induced to very high levels of expression following T cell and macrophage activation and following infection with HIV. The induction of 9145 may lead to increased cortisol levels locally and perhaps systemically which could lead to reduced immune responses including the production of proinflammatory cytokines, cytotoxic T cell and NK cell killing of virus-infected cells and enhanced viral replication. Therefore, inhibition of 9145 may decrease glucocorticoid levels, inhibit HIV replication and prevent the immunosuppressive effects of cortisol.

[0016] Due to 9145 mRNA expression in thymocytes, dendritic cells, dendritic cell CD4+ T cell (DC/CD4) cocultures, T cells and macrophages, along with its functional role, modulators of 9145 activity would be useful in treating AIDS and HIV-related disorders. 9145 polypeptides of the present invention are useful to screen for modulators of 9145 activity.

#### **Gene ID 1725**

[0017] The human 1725 sequence (SEQ ID NO:3), known also as angiotensin-converting enzyme, testis-specific isoform (ACE-T), is approximately 2478 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 29 to 2227 of SEQ ID NO:3, encodes a 732 amino acid protein (SEQ ID NO:4).

[0018] As assessed by TaqMan analysis, 1725 mRNA was highly expressed in macrophages, PBMC, tonsil and lymph node. 1725 mRNA was induced by HIV infection of CD4+ T cells, thymocytes, dendritic cells, dendritic cell/CD4+ T co-cultures and was highly expressed in the permissive Jurkat T cell clone 10H.

[0019] 1725 is a protease that is expressed at high levels in lymphocytes, dendritic cells and macrophages. 1725 is induced in macrophages by CD4+T cells (*Clin Exp Immunol*, 1992, 88(2):288-94) and is known to be involved in activation of CD4+ T cells. 1725 also has high levels of expression in lymphocytes, dendritic cells and macrophages when induced by HIV infection. 1725 is involved in T cell activation required for HIV replication. Therefore, antagonizing 1725 would inhibit HIV replication.

[0020] Due to 1725 mRNA expression in macrophages, PBMC, tonsil and lymph node, along with its functional role, modulators of 1725 activity would be useful in treating AIDS and HIV-related disorders. 1725 polypeptides of the present invention are useful to screen for modulators of 1725 activity.

**Gene ID 311**

[0021] The human 311 sequence (SEQ ID NO:5), known also as the nicotinic acid receptor (HM74A), is approximately 2051 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 61 to 1224 of SEQ ID NO:5, encodes a 387 amino acid protein (SEQ ID NO:6).

[0022] As assessed by TaqMan analysis, 311 mRNA was highly expressed in spleen, tonsil, lymph node and PBMC. 311 mRNA was induced by HIV infection of dendritic cells, dendritic cell/T cell co-cultures and macrophages.

[0023] 311 is the nicotinic acid receptor, HM74A (*JBC*, 2003, 278:9869-9874). Administration of nicotinic acid is used in the treatment of dyslipidemia which is believed to inhibit adipocyte lipolysis via the activation of a Gi-coupled receptor. Gi-coupled receptor stimulation results in the activation of MAP and JNK kinases which are involved in the production of cytokines and cell division. HIV replication requires T cell activation. Antagonizing 311 would result in decreased T cell activation and viral replication.

[0024] Due to 311 mRNA expression in the spleen, tonsil, lymph node and PBMC, along with its functional role, modulators of 311 activity would be useful in treating AIDS and HIV-related disorders. 311 polypeptides of the present invention are useful to screen for modulators of 311 activity.

**Gene ID 837**

[0025] The human 837 sequence (SEQ ID NO:7), known also as the alpha 7 subunit of the acetylcholine receptor, is approximately 2087 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 104 to 1612 of SEQ ID NO:7, encodes a 502 amino acid protein (SEQ ID NO:8).

[0026] As assessed by TaqMan analysis, 837 mRNA was highly expressed in peripheral blood lymphocytes (PBL) and tonsil. 837 mRNA was induced by HIV infection of CD4+ T cells, thymocytes, dendritic cells, dendritic cell/CD4+ T co-cultures.

[0027] 837 is required for an anti-inflammatory response that inhibits TNF $\alpha$  secretion by macrophages (*Nature*, May 2000, 405(6785):458-462). 837 knockouts display elevated levels of TNF $\alpha$ . TNF $\alpha$  is secreted by macrophages, which enhances HIV replication in a paracrine fashion. Agonizing 837 will reduce the level of TNF $\alpha$  secreted by macrophages, resulting in reduced HIV replication.

[0028] Due to 837 mRNA expression in the PBL and tonsil, along with its functional role, modulators of 837 activity would be useful in treating AIDS and HIV-related disorders. 837 polypeptides of the present invention are useful to screen for modulators of 837 activity.

#### **Gene ID 58305**

[0029] The human 58305 sequence (SEQ ID NO:9), known also as vesicular inhibitory amino acid transporter (GABA and glycine) (hVIAAT), is approximately 2585 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 248 to 1825 of SEQ ID NO:9, encodes a 525 amino acid protein (SEQ ID NO:10).

[0030] As assessed by transcriptional profiling, 58305 mRNA expression was up regulated in PBMCs of SIV infected rhesus macaque monkeys. This was confirmed by RT-PCR.

[0031] T lymphocyte activation is required for viral replication. Activated T cells are highly metabolically active and undergo multiple rounds of cell division. Each cell division requires a doubling of cellular proteins, requiring increased cellular uptake of amino acids for protein synthesis. During HIV replication up to thirty percent of total cellular mRNA can be viral transcripts resulting in high levels of viral protein synthesis. Therefore, inhibition of 58305 will inhibit T cell activation and viral protein synthesis resulting in decreased viral replication.

[0032] Due to 58305 mRNA expression in HIV-infected T-cells, along with its functional role, modulators of 58305 activity would be useful in treating AIDS and HIV-related disorders. 58305 polypeptides of the present invention are useful to screen for modulators of 58305 activity.

#### **Gene ID 156**

[0033] The human 156 sequence (SEQ ID NO:11), known also as formyl peptide receptor-like 2 (FPRL2), is approximately 1062 nucleotides long. The coding sequence, located at about nucleic acid 1 to 1062 of SEQ ID NO:11, encodes a 353 amino acid protein (SEQ ID NO:12).

[0034] As assessed by transcriptional profiling, 156 mRNA expression was up regulated in dendritic cell/CD4+ T cell cocultures. TaqMan analysis indicated that 156 mRNA was expressed at relatively low levels in most tissues and was expressed at higher

levels in dendritic cell/CD4+ T cells and macrophages. 156 mRNA was also up regulated in HIV infected macrophages, primary CD4+ T lymphocytes, thymocytes and T cells.

[0035] Immature dendritic cells (iDC) respond chemotactically and by Ca(2+) mobilization to N-formyl-Met-Leu-Phe and a recently identified synthetic peptide Trp-Lys-Tyr-Met-Val-D-Met (WKYMVm; SEQ ID NO:53), whereas mature dendritic cells (mDC) derived from the same donor only respond to WKYMVm. Furthermore, iDC and mDC express FPRL2 mRNA and protein. As mDC do not express any other members of the human FPR subfamily, FPRL2 expressed by DC must be functional and mediate the effect of WKYMVm on DC (*J Leukoc Biol*, 2002 Sep;72(3):598-607).

[0036] Stimulation of GPCRs, including 156 which is Gi linked, leads to T cell activation and proliferation. HIV replication requires T cell activation. FPRL2, expressed in myeloid DC, maintains its maturation, suggesting that the interaction of FPRL2 and its endogenous ligand(s) may be involved in regulating DC trafficking during antigen uptake and processing in the periphery as well as the T cell-stimulating phase of immune responses. Therefore antagonizing 156 would provide a means to inhibit T cell activation and HIV replication.

[0037] Due to 156 mRNA expression in T lymphocytes and T cell lines, along with its functional role, modulators of 156 activity would be useful in treating AIDS and HIV-related disorders. 156 polypeptides of the present invention are useful to screen for modulators of 156 activity.

#### **Gene ID 14175**

[0038] The human 14175 sequence (SEQ ID NO:13), known also as serine/threonine protein kinase 10 or lymphocyte-oriented kinase (LOK), is approximately 4221 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 51 to 2957 of SEQ ID NO:13, encodes a 968 amino acid protein (SEQ ID NO:14).

[0039] As assessed by TaqMan analysis, 14175 mRNA expression was detected in lymphocytes of SIV infected rhesus macaques. TaqMan analysis of an organ recital panel indicated 14175 mRNA was highly expressed in PBMCs compared to other organs. TaqMan analysis of an inflammation panel also confirmed expression of 14175 mRNA in lymphocytes and monocytes.

[0040] T lymphocyte activation is required for viral replication. A number of kinases are involved in T cell activation following stimulation through the T cell receptor.

14175 is a new and unique member of the STE20 family with serine/threonine kinase activity and its expression is restricted mostly to lymphoid cells (*Immunogenetics*, 1999 May;49(5):369-75). 14175 is involved in mitogen-activated protein (MAP) kinase cascades, which is induced by viral replication. 14175 gene expression is slightly induced in response to T cell activation and HIV infection, suggesting that 14175 is required for viral replication. Therefore, antagonizing 14175 will inhibit T cell activation and viral replication.

[0041] Due to 14175 mRNA expression in lymphocytes and PBMCs, along with its functional role, modulators of 14175 activity would be useful in treating AIDS and HIV-related disorders. 14175 polypeptides of the present invention are useful to screen for modulators of 14175 activity.

#### **Gene ID 50352**

[0042] The human 50352 sequence (SEQ ID NO:15), known also as a ubiquitin transferase, is approximately 3513 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 82 to 3150 of SEQ ID NO:15, encodes a 1022 amino acid protein (SEQ ID NO:16).

[0043] As assessed by TaqMan analysis, 50352 mRNA expression was up regulated in HIV infected dendritic cell/CD4 + T cell cocultures. TaqMan analysis of organ recital panels indicated high expression of 50352 mRNA in PBMCs and macrophages. RT-PCR of HIV infected PBMCs, monocytes and the T cell line CEM indicated increased expression of 50352 mRNA.

[0044] Ubiquitin transferases catalyze the addition of ubiquitin to cellular proteins resulting in degradation by the proteosome. Many molecules necessary for transcription of the HIV genome require ubiquitin transferases for regulation, including NFkB. T lymphocyte activation also requires ubiquitin transferases for regulation which is required for viral replication. 50352 is required for processing of HIV Gag proteins.

Ubiquitination of cellular proteins precedes degradation or processing of proteins by 50352. Therefore, inhibition of 50352 inhibits T cell activation and viral replication.

[0045] Due to 50352 mRNA expression in dendritic cell/CD4 + T cell cocultures and T cell lines, along with its functional role, modulators of 50352 activity would be useful in treating AIDS and HIV-related disorders. 50352 polypeptides of the present invention are useful to screen for modulators of 50352 activity.

**Gene ID 32678**

[0046] The human 32678 sequence (SEQ ID NO:17), known also as an acid-sensing channel (ASIC1), is approximately 3923 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 230 to 1954 of SEQ ID NO:17, encodes a 574 amino acid protein (SEQ ID NO:18).

[0047] As assessed by transcriptional profiling, 32678 mRNA expression was up regulated in HIV infected thymocytes and the T cell line C8166. TaqMan analysis confirmed increased expression of 32678 mRNA in HIV infected primary macrophages at multiple time points. 32678 mRNA expression was dramatically increased at the peak of infection of two T lymphocyte cell lines, H9 and C8166.

[0048] 32678 or ASIC1 is an acid-sensing channel that is permeable to calcium and will cause depolarization of the cell membrane. Depolarization of the cell membrane will open voltage sensitive calcium channels (VSCC's) leading to increased accumulation of intracellular calcium. (*Nature*, 1997 Mar 13;386(6621):173-7). Calcium is an important intracellular messenger that is released from intracellular storage compartments and from plasma membrane  $Ca^{++}$  channels following the generation of inositol triphosphate (InsP3). InsP3 is involved in signaling through the T cell receptor (TCR)/CD3 complex resulting in T cell activation (*Cell*, 1989 Oct 6;59(1):15-20). T cell activation through the TCR/CD3 complex is required for HIV replication in T lymphocytes. Therefore, antagonizing 32678 may inhibit signaling through the TCR/CD3 complex resulting in decreased T cell activation and HIV replication.

[0049] Due to 32678 mRNA expression in HIV-infected T cells, along with its functional role, modulators of 32678 activity would be useful in treating AIDS and HIV-related disorders. 32678 polypeptides of the present invention are useful to screen for modulators of 32678 activity.

**Gene ID 5560**

[0050] The human 5560 sequence (SEQ ID NO:19), known also as aspartyl protease 3, is approximately 1373 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 31 to 1373 of SEQ ID NO:19, encodes a 448 amino acid protein (SEQ ID NO:20).

[0051] As assessed by transcriptional profiling, 5560 mRNA expression increased in HIV infected thymocytes and primary CD4+ T cells. 5560 mRNA expression was highly restricted to T cells and lymphoid tissue and is further induced upon T cell activation and HIV infection. Increased 5560 mRNA expression in HIV infected thymocytes, CD4+ T cells, dendritic cells, monocytes and the T cell line ACH2 was confirmed by TaqMan analysis.

[0052] 5560 is an aspartyl protease. 5560 is greatly induced following HIV infection suggesting that this enzyme is required for efficient viral replication. Some cellular proteases are known to cleave the HIV gap-pol protein precursor. Inhibition of 5560 may inhibit HIV replication.

[0053] Due to 5560 mRNA expression in HIV-infected thymocytes and T cells, along with its functional role, modulators of 5560 activity would be useful in treating AIDS and HIV-related disorders. 5560 polypeptides of the present invention are useful to screen for modulators of 5560 activity.

#### **Gene ID 7240**

[0054] The human 7240 sequence (SEQ ID NO:21), known also as aldehyde dehydrogenase 1 (ALDH1) or retinal dehydrogenase 1, is approximately 1506 nucleotides long. The coding sequence, located at about nucleic acid 1 to 1506 of SEQ ID NO:21, encodes a 501 amino acid protein (SEQ ID NO:22).

[0055] As assessed by transcriptional profiling, 7240 mRNA expression was up regulated in HIV infected dendritic cell/CD4+ T cell cocultures (DC/TC). RT-PCR confirmed expression in HIV infected DC/TC, macrophages and the T cell line ACH2.

[0056] Metabolism of retinaldehyde to retinoic acid (RA) is tissue-restricted and ALDH1 is expressed at high levels in DC/TC, macrophages and the T cell line ACH2. ALDH1 is required to metabolize retinol to RA to initiate retinoid signaling. (*Chem Biol Interact*, 2003 Feb 1;143-144:201-10). Retinoic acid receptor alpha (RXR $\alpha$ ) stimulates transcription from the HIV LTR by binding to the nuclear receptor-responsive element in the presence of RA. Inhibitors of ALDH1 would prevent the conversion of retinaldehyde to RA and prevent RXR $\alpha$  stimulated transcription from the HIV LTR resulting in decreased HIV replication. An FDA approved small molecule inhibitor of ALDH1 exists (disulfiram). (*J. Biol. Chem.*, Feb 1994; 269:5944 – 5951).

[0057] Due to 7240 mRNA expression in HIV infected DC/TC, along with its functional role, modulators of 7240 activity would be useful in treating AIDS and HIV-



related disorders. 7240 polypeptides of the present invention are useful to screen for modulators of 7240 activity.

#### **Gene ID 8865**

[0058] The human 8865 sequence (SEQ ID NO:23), known also as transglutaminase 2 (TGase), is approximately 3257 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 136 to 2199 of SEQ ID NO:23, encodes a 687 amino acid protein (SEQ ID NO:24).

[0059] As assessed by transcriptional profiling, 8865 mRNA expression was deregulated in gene arrays of HIV infection of dendritic cell/T cell cocultures (DC/TC). RT-PCR confirms expression of 8865 mRNA in HIV infected T cell lines, macrophages, primary CD4+ cells and DC/TC.

[0060] TGase cross links polyamines to target proteins, and is regulated by the GTP binding activity of TGase. (*J. Biol. Chem.*, January 3, 2003, 278(1):391-399). The transamidation reaction of TGase has been implicated in a number of biological processes including cellular differentiation, and apoptosis. Mitogens, tumor promoters, and cell differentiation inducing agents trigger an intracellular signaling cascade, which involves Ras and Rho GTPases and leads to activation of mitogen-activated protein (MAP) kinases. HIV is also known to induce cellular signaling pathways including MAP kinases. Retinoic acid (RA) promotes activation of TGase and *in vivo* transamidation of RhoA. RhoA binds/activates RhoA-associated kinase-2 (ROCK-2), a downstream target and an effector of GTP-bound RhoA which promotes activation of MAP/ERK kinases leading to regulation of nuclear events. Inhibition of TGase would prevent the Rho GTPase activation of MAP/ERK kinases resulting in decreased HIV replication.

[0061] Due to 8865 mRNA expression in HIV infected T cell lines, macrophages, primary CD4+ cells and DC/TC, along with its functional role, modulators of 8865 activity would be useful in treating AIDS and HIV-related disorders. 8865 polypeptides of the present invention are useful to screen for modulators of 8865 activity.

#### **Gene ID 12396**

[0062] The human 12396 sequence (SEQ ID NO:25), known also as the GPCR GPR41, is approximately 1061 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 11 to 1051 of SEQ ID NO:25, encodes a 346 amino acid protein (SEQ ID NO:26).

[0063] As assessed by transcriptional profiling, 12396 mRNA expression was restricted primarily to leukocytes. RT-PCR indicated increased 12396 mRNA expression in HIV infected macrophages, dendritic cells, the T cell line ACH2 and in T cells stimulated with antibodies to CD3.

[0064] Propionate was the most potent agonist for GPR41. The receptor is coupled to Inositol 1,4,5-trisphosphate (IP3) formation, intracellular Ca<sup>2+</sup> release, ERK1/2 activation and inhibition of cyclic adenosine monophosphate (cAMP) accumulation. GPR41 is coupled exclusively through the Pertussis toxin-sensitive Gi/o family (*J. Biol. Chem.* 2003 Apr 23; [epub ahead of print]). HIV replication requires T cell activation which requires cAMP accumulation. Agonizing this receptor would result in the inhibition of cAMP accumulation and decreased HIV replication which would be beneficial in the treatment of HIV infection.

[0065] Due to 12396 mRNA expression in HIV infected macrophages, dendritic cells, the T cell line ACH2 and in T cells stimulated with antibodies to CD3, along with its functional role, modulators of 12396 activity would be useful in treating AIDS and HIV-related disorders. 12396 polypeptides of the present invention are useful to screen for modulators of 12396 activity.

#### **Gene ID 12397**

[0066] The human 12397 sequence (SEQ ID NO:27), known also as GPCR GPR43, is approximately 1013 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 11 to 1003 of SEQ ID NO:27, encodes a 330 amino acid protein (SEQ ID NO:28).

[0067] As assessed by transcriptional profiling, 12397 mRNA expression was restricted primarily to leukocytes. RT-PCR indicated increased 12397 mRNA expression in HIV infected macrophages, dendritic cells and the T cell line ACH2.

[0068] Propionate was the most potent agonist for GPR43. The receptor is coupled to IP3 formation, intracellular Ca<sup>2+</sup> release, ERK1/2 activation and increased cAMP accumulation. GPR43 displayed a dual coupling through Gi/o and Pertussis toxin-insensitive Gq protein families. GPCR 43 is believed to be involved in the induction of proinflammatory immune responses. (*J. Biol. Chem.* 2003 Apr 23; [epub ahead of print]). HIV infection is characterized by high level immune activation which correlates with disease progression. Therapies targeting immune activation have shown efficacy in the

treatment of HIV in humans. Antagonizing this receptor would prevent activation of the immune response by leukocytes and inhibit HIV infection.

[0069] Due to 12397 mRNA expression in HIV infected macrophages, dendritic cells and the T cell line ACH2, along with its functional role, modulators of 12397 activity would be useful in treating AIDS and HIV-related disorders. 12397 polypeptides of the present invention are useful to screen for modulators of 12397 activity.

#### **Gene ID 13644**

[0070] The human 13644 sequence (SEQ ID NO:29), known also as monocarboxylate transporter 4 (MCT 4), is approximately 1982 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 63 to 1460 of SEQ ID NO:29, encodes a 465 amino acid protein (SEQ ID NO:30).

[0071] As assessed by transcriptional profiling, 13644 mRNA was highly expressed in T cells and macrophages. 13644 mRNA was expressed at higher levels in HIV permissive macrophages when compared to nonpermissive macrophages. HIV infection induced 13644 mRNA expression in macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC).

[0072] MCT4 is most evident in white muscle and other cells with a high glycolytic rate, such as tumor cells and white blood cells, suggesting it is expressed where lactic acid efflux predominates (*Biochem. J.*, 1999, 343:281-299). T cell activation is required for efficient HIV replication. Activated T cells generate the majority of energy needs via glycolysis. Inhibition of MCT4 would lower the level of T cell activation by inhibition of lactic acid efflux, resulting in inhibition of HIV replication (*Biochem. J.*, 1999, 343:281-299).

[0073] Due to 13644 mRNA expression in HIV infected macrophages, dendritic cells and T cells, along with its functional role, modulators of 13644 activity would be useful in treating AIDS and HIV-related disorders. 13644 polypeptides of the present invention are useful to screen for modulators of 13644 activity.

#### **Gene ID 19938**

[0074] The human 19938 sequence (SEQ ID NO:31), known also as kynurenine 3-hydroxylase, is approximately 1999 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 53 to 1513 of SEQ ID NO:31, encodes a 486 amino acid protein (SEQ ID NO:32).

[0075] As assessed by transcriptional profiling, 19938 mRNA expression was up regulated in HIV infected dendritic cell/CD4+ cell co-cultures (DC/TC). RT-PCR analysis confirmed expression in DC, DC/TC and monocytes.

[0076] IDO (Indoleamine 2,3-dioxygenase) catalyzes the degradation of tryptophan to kynurenine and subsequent catabolic byproducts. IDO is implicated in the induction of T cell tolerance. Local decreases in availability of tryptophan and the presence of its catabolic byproducts inhibit T cell proliferation and may induce apoptotic death (*Nature Immunology*, 2002, 3:1056-1057). 19938 converts kynurenine to hydroxykynurenine. 19938 mRNA expression is induced in HIV infected DC and DC/TC.

[0077] The induction of this enzyme may have a direct effect of HIV infection. T cell tolerance is seen in patients with HIV infection. Increased levels of apoptosis are also seen in human and primate models of pathogenic HIV and SIV infection. The reduction in tryptophan levels and the accumulation of kynurenine may be responsible for increased T cell tolerance as well as increased levels of apoptosis in HIV infected and noninfected T lymphocytes. Therefore, inhibition of 19938 may prevent T cell tolerance and the increased apoptosis of T lymphocytes seen in patients with HIV infection.

[0078] Due to 19938 mRNA expression in HIV infected dendritic cell/CD4+ cell co-cultures (DC/TC), along with its functional role, modulators of 19938 activity would be useful in treating AIDS and HIV-related disorders. 19938 polypeptides of the present invention are useful to screen for modulators of 19938 activity.

#### Gene ID 2077

[0079] The human 2077 sequence (SEQ ID NO:33), known also as glomerular epithelial protein 1 (GLEPP1) or protein-tyrosine-phosphatase receptor type O precursor, is approximately 5415 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 173 to 3739 of SEQ ID NO:33, encodes an 1188 amino acid protein (SEQ ID NO:34).

[0080] As assessed by transcriptional profiling, 2077 mRNA was highly expressed in dendritic cells and macrophages. HIV infection induced 2077 mRNA expression in macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC).

[0081] 2077 is induced by HIV infection suggesting a role in viral replication. 2077 may dephosphorylate cellular proteins involved in inhibition of replication. If this phosphatase enhances viral replication, then antagonizing 2077 would inhibit HIV replication.

[0082] Due to 2077 mRNA expression in HIV infected macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC), along with its functional role, modulators of 2077 activity would be useful in treating AIDS and HIV-related disorders. 2077 polypeptides of the present invention are useful to screen for modulators of 2077 activity.

#### **Gene ID 1735**

[0083] The human 1735 sequence (SEQ ID NO:35), known also as matrix metalloproteinase-9 (MMP-9), is approximately 2373 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 6 to 2129 of SEQ ID NO:35, encodes a 707 amino acid protein (SEQ ID NO:36).

[0084] As assessed by transcriptional profiling, 1735 mRNA expression increased in HIV infected macrophages and dendritic cells. 1735 mRNA expression was highly restricted to macrophages and dendritic cells and was further induced upon HIV infection. Increased 1735 mRNA expression in HIV infected macrophages and in dendritic cells was confirmed by TaqMan analysis.

[0085] 1735 is a matrix metalloprotease. 1735 is greatly induced following HIV infection suggesting that this enzyme is required for efficient viral replication. MMP9 is associated with immune activation and may affect leukocyte entry into the brain. (*J Virol.* 2001 Jul; 75(14):6572-83). Inhibition of MMP-9 may result in decreased viral replication as well as decreased HIV associated neuropathy.

[0086] Due to 1735 mRNA expression in HIV infected macrophages and dendritic cells, along with its functional role, modulators of 1735 activity would be useful in treating AIDS and HIV-related disorders. 1735 polypeptides of the present invention are useful to screen for modulators of 1735 activity.

#### **Gene ID 1786**

[0087] The human 1786 sequence (SEQ ID NO:37), known also as granzyme B, is approximately 934 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 8 to 751 of SEQ ID NO:37, encodes a 247 amino acid protein (SEQ ID NO:38).

[0088] As assessed by transcriptional profiling, 1786 mRNA expression increased in HIV infected thymocytes and primary CD4+ T cells as well as in a Jurkat T cell clone highly permissive to infection. 1786 mRNA expression was highly restricted to T cells

and lymphoid tissue and was further induced upon T cell activation and HIV infection. Increased 1786 mRNA expression in HIV infected thymocytes, CD4+ T cells, and in the Jurkat T cell line was confirmed by TaqMan analysis.

[0089] Granzyme B is a T cell- and natural killer cell-specific trypsin-like serine protease that is released from effector cells during cytotoxic cell killing. Granzyme B is essential for the induction of DNA fragmentation and apoptosis in target cells. Granzyme B is found in the blood of normal individuals and at increased levels in patients with rheumatoid arthritis and acute EBV and HIV infection suggesting that granzymes have additional biological effects. Granzyme B is known to induce IL-6 and IL-8 production in fibroblasts and stimulates IL-6, IL-8 and TNF-alpha from monocytes. (*J Immunol.* 1998 Apr 1; 160(7):3610-3616). Proinflammatory cytokines contribute to increased levels of immune activation and viral replication, therefore inhibition of Granzyme B should inhibit HIV replication.

[0090] Due to 1786 mRNA expression in HIV infected thymocytes, CD4+ T cells, and in the Jurkat T cell line, along with its functional role, modulators of 1786 activity would be useful in treating AIDS and HIV-related disorders. 1786 polypeptides of the present invention are useful to screen for modulators of 1786 activity.

#### **Gene ID 10220**

[0091] The human 10220 sequence (SEQ ID NO:39), known also as ionotropic purinergic receptor P2X7, is approximately 1853 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 27 to 1814 of SEQ ID NO:39, encodes a 595 amino acid protein (SEQ ID NO:40).

[0092] 10220 was identified in a transcriptional profile of HIV infected monocytes. It was expressed in most tissues and was expressed at higher levels in monocytes, dendritic cells, thymocytes, T lymphocytes and macrophages. 10220 mRNA expression was up regulated following HIV infection in macrophages as confirmed by RT-PCR.

[0093] P2X7 is a human purinoceptor 7 (ATP receptor) which facilitates cation channel activation and secretion of IL-1beta from LPS-primed macrophages (*J. Immunol.* 2003 Jun 1; 170(11):5728-38). HIV replication in macrophages stimulates IL-1 production in vivo and in vitro which acts in an autocrine and paracrine manner to enhance HIV replication in T cells and monocytes. Antibodies to IL-1 inhibit the enhanced HIV

replication due to IL-1 production in vitro. P2X7 knockout mice are healthy and fertile. Absence of the P2X7R thus leads to an inability of peritoneal macrophages to release IL-1 in response to ATP. (*J. Biol. Chem.*, January 5, 2001; 276(1):125-132). Inhibition of P2X7 dependent IL-1 production would decrease HIV replication and would not have deleterious effects as demonstrated by the knockout mice.

[0094] Due to 10220 mRNA expression in HIV infected monocytes and macrophages, along with its functional role, modulators of 10220 activity would be useful in treating AIDS and HIV-related disorders. 10220 polypeptides of the present invention are useful to screen for modulators of 10220 activity.

#### **Gene ID 17822**

[0095] The human 17822 sequence (SEQ ID NO:41), a dipeptidase similar to microsomal dipeptidase precursor 1 (MDP1), is approximately 1700 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 125 to 1585 of SEQ ID NO:41, encodes a 486 amino acid protein (SEQ ID NO:42).

[0096] As assessed by TaqMan analysis, 17822 mRNA was highly expressed in dendritic cells and macrophages. 17822 mRNA expression was induced to higher levels in HIV permissive vs. nonpermissive macrophages. HIV infection induced 17822 mRNA expression in macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC).

[0097] 17822 is a membrane-bound dipeptidase. 17822 catalyzes the conversion of leukotriene D4 (LTD4) to leukotriene E4 (LTE4). (*The FASEB Journal*. 2003; 17:1313-1315). 17822 may also participate in immune/inflammatory processes involving leukotrienes which are elevated in patients with asthma and may play a role in pathogenesis. Proinflammatory molecules enhance HIV infection and it is possible that LTE4 may enhance replication, therefore inhibition of 17822 should inhibit viral replication.

[0098] Due to 17822 mRNA expression in HIV infected macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC), along with its functional role, modulators of 17822 activity would be useful in treating AIDS and HIV-related disorders. 17822 polypeptides of the present invention are useful to screen for modulators of 17822 activity.

#### **Gene ID 33945**

[0099] The human 33945 sequence (SEQ ID NO:43), known as UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 12 (GalNAc-T12), is approximately 2850 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 81 to 1826 of SEQ ID NO:43, encodes a 581 amino acid protein (SEQ ID NO:44).

[0100] 33945 was identified by transcriptional profiling of HIV infected monocytes. 33945 mRNA was highly expressed in T cells, dendritic cells and macrophages and was further induced upon HIV infection of monocytes, as confirmed by TaqMan analysis.

[0101] GalNAc-T12 is involved in O-linked glycosylation of many substrates including the V3 loop of HIV envelope. (*FEBS Lett.*, 2002 Jul 31; 524(1-3):211-8). 33945 is greatly induced following HIV infection suggesting that this enzyme is required for efficient viral replication. Glycosylation of the HIV envelope is required for infectivity. Inhibitors of 33945 would inhibit the infectivity of HIV by preventing O-linked glycosylation of the V3 loop of HIV envelope.

[0102] Due to 33945 mRNA expression in HIV infected monocytes, along with its functional role, modulators of 33945 activity would be useful in treating AIDS and HIV-related disorders. 33945 polypeptides of the present invention are useful to screen for modulators of 33945 activity.

#### **Gene ID 43748**

[0103] The human 43748 sequence (SEQ ID NO:45), known also as aquaporin 9 (AQP9), is approximately 2890 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 229 to 1116 of SEQ ID NO:45, encodes a 295 amino acid protein (SEQ ID NO:46).

[0104] As assessed by TaqMan analysis, 43748 mRNA was highly expressed in dendritic cells and macrophages. 43748 mRNA expression was increased in HIV permissive vs. nonpermissive macrophages. HIV infection induced 43748 mRNA expression in macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC).

[0105] AQP9 is most evident in white muscle and other cells with a high glycolytic rate, such as tumor cells and white blood cells, suggesting it is expressed where lactic acid efflux predominates. T cell activation is required for efficient HIV replication. Activated T cells generate the majority of their energy needs via glycolysis. AQP9 is most predominant in white blood cells and it transports glycerol and urea at physiological pH.



(*Proc Natl Acad Sci USA*, 2003 Mar 4; 100(5):2945-50.; E pub 2003 Feb 19). Inhibition of AQP9 would lower the level of T cell metabolic activity by inhibition of transport of glycerol and urea, resulting in inhibition of HIV replication.

[0106] Due to 43748 mRNA expression in HIV infected macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC), along with its functional role, modulators of 43748 activity would be useful in treating AIDS and HIV-related disorders. 43748 polypeptides of the present invention are useful to screen for modulators of 43748 activity.

#### **Gene ID 47161**

[0107] The human 47161 sequence (SEQ ID NO:47), known also as N-acetylgalactosaminyltransferase 6 (GalNAc-T6), is approximately 1869 nucleotides long. The coding sequence, located at about nucleic acid 1 to 1869 of SEQ ID NO:47, encodes a 622 amino acid protein (SEQ ID NO:48).

[0108] 47161 was identified by transcriptional profiling of HIV infected monocytes. 47161 mRNA expression was very restricted and was highly expressed in T cells, dendritic cells and macrophages and is further induced upon HIV infection of monocytes, as confirmed by TaqMan analysis.

[0109] GalNAc-T6 is involved in O-linked glycosylation of many substrates including the V3 loop of HIV envelope. (*J Biol Chem.*, 1999 Sep 3; 274(36):25362-70). 47161 is greatly induced following HIV infection suggesting that this enzyme is required for efficient viral replication. Glycosylation of the HIV envelope is required for infectivity. Inhibitors of 47161 would inhibit the infectivity of HIV by preventing O-linked glycosylation of the V3 loop of HIV envelope.

[0110] Due to 47161 mRNA expression in HIV infected monocytes, along with its functional role, modulators of 47161 activity would be useful in treating AIDS and HIV-related disorders. 47161 polypeptides of the present invention are useful to screen for modulators of 47161 activity.

#### **Gene ID 81982**

[0111] The human 81982 sequence (SEQ ID NO:49), known also as "probable serine protease HTRA4 precursor", is approximately 1544 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 87 to 1517 of SEQ ID NO:49, encodes a 476 amino acid protein (SEQ ID NO:50).

[0112] As assessed by transcriptional profiling, 81982 mRNA expression was increased in HIV infected macrophages and dendritic cells. 81982 mRNA expression was highly restricted to macrophages and dendritic cells and was further induced upon HIV infection. Increased 81982 mRNA expression in HIV infected macrophages and dendritic cells was confirmed by TaqMan analysis.

[0113] 81982 is a serine protease. 81982 is greatly induced following HIV infection suggesting that this enzyme is required for efficient viral replication. 5-hydroxytryptamine (serotonin) receptor 4 (HTr4) is in the secretory pathway and is involved in degrading damaged proteins and signal peptides found on HIV proteins. High level protein synthesis occurs during HIV replication. These proteins accumulate inside the cell membrane and assemble to form virions. In vivo, aggregate formation is a highly favorable process due to the extremely high intracellular protein concentrations. HTr4 is a protease-chaperone heat shock protein that prevents aggregate formation (*Molecular Cell*, Sept. 2002; 10:443-455). Inhibition of this enzyme may interfere with virion protein assembly, maturation and release of viral particles.

[0114] Due to 81982 mRNA expression in HIV infected macrophages and dendritic cells, along with its functional role, modulators of 81982 activity would be useful in treating AIDS and HIV-related disorders. 81982 polypeptides of the present invention are useful to screen for modulators of 81982 activity.

#### Gene ID 46777

[0115] The human 46777 sequence (SEQ ID NO:51), known also as disintegrin-protease, is approximately 2187 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 61 to 1473 of SEQ ID NO:51, encodes a 470 amino acid protein (SEQ ID NO:52).

[0116] As assessed by transcriptional profiling, 46777 mRNA expression levels increased in HIV infected thymocytes and primary DC/TC (dendritic cell/T cell cocultures) compared to non-infected samples. 46777 tissue expression was highly restricted to T cells and lymphoid tissue and was further induced upon T cell activation and HIV infection. TaqMan experiments additionally confirmed that 46777 mRNA expression was increased in HIV infected thymocytes, dendritic cells, and monocytes.

[0117] 46777 is a protease which is greatly induced following HIV infection, suggesting that this enzyme is required for efficient viral replication. Some cellular

proteases are known to cleave the HIV gap-pol protein precursor. Therefore, inhibition of 46777 should inhibit HIV replication.

[0118] Therefore, based on the specific expression and regulation of 46777 in HIV infected tissues and cell types, such thymocytes and T cells, modulators of 46777 activity would be useful in treating AIDS or an HIV-related disorder. 46777 polypeptides of the present invention would be useful in screening for modulators of 46777 activity.

[0119] Various aspects of the invention are described in further detail in the following subsections:

I. Screening Assays:

**[0120]** The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules (organic or inorganic) or other drugs) which bind to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins, have a stimulatory or inhibitory effect on, for example, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity, or have a stimulatory or inhibitory effect on, for example, the expression or activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate. Compounds identified using the assays described herein may be useful for treating AIDS or an HIV-related disorder.

**[0121]** These assays are designed to identify compounds that bind to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, bind to other intracellular or extracellular proteins that interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, and interfere with the interaction of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein with other intercellular or extracellular proteins. For example, in the case of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, which is a transmembrane receptor-type protein, such techniques can identify ligands for such a receptor. A 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein ligand or substrate can, for example, be used to ameliorate at least one symptom of AIDS or an HIV-related disorder. Such compounds may include, but are not limited to peptides, antibodies, or small organic or inorganic compounds. Such compounds may also include other cellular proteins.

[0122] Compounds identified via assays such as those described herein may be useful, for example, for treating AIDS or an HIV-related disorder. In instances whereby AIDS or an HIV-related disorder results from an overall lower level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression and/or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein in a cell or tissue, compounds that interact with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein may include compounds which accentuate or amplify the activity of the bound 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Such compounds would bring about an effective increase in the level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein activity, thus ameliorating symptoms.

[0123] In other instances, mutations within the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene may cause aberrant types or excessive amounts of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins to be made which have a deleterious effect that leads to AIDS or an HIV-related disorder. Similarly, physiological conditions may cause an excessive increase in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression leading to AIDS or an HIV-related disorder. In such cases, compounds that bind to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein may be identified that inhibit the activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Assays for testing the effectiveness of compounds identified by techniques such as those described in this section are discussed herein.

[0124] In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or polypeptide or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or polypeptide or biologically active portion thereof. The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution-phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997) *Anticancer Drug Des.* 12:145).

[0125] Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994) *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

[0126] Libraries of compounds may be presented in solution (*e.g.*, Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (Ladner USP 5,223,409), spores (Ladner USP '409), plasmids (Cull *et al.* (1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith (1990) *Science* 249:386-390); (Devlin (1990) *Science* 249:404-406); (Cwirla *et al.* (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382); (Felici (1991) *J. Mol. Biol.* 222:301-310); (Ladner *supra.*).

[0127] In one embodiment, an assay is a cell-based assay in which a cell which expresses a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate 9145, 1725, 311, 837, 58305,

156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is determined. Determining the ability of the test compound to modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity can be accomplished by monitoring, for example, intracellular calcium, IP<sub>3</sub>, cAMP, or diacylglycerol concentration, the phosphorylation profile of intracellular proteins, cell proliferation and/or migration, gene expression of, for example, cell surface adhesion molecules or genes associated with AIDS or an HIV-related disorder, or the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -regulated transcription factor. The cell can be of mammalian origin, *e.g.*, a neural cell. In one embodiment, compounds that interact with a receptor domain can be screened for their ability to function as ligands, *i.e.*, to bind to the receptor and modulate a signal transduction pathway. Identification of ligands, and measuring the activity of the ligand-receptor complex, leads to the identification of modulators (*e.g.*, antagonists) of this interaction. Such modulators may be useful in the treatment of AIDS or an HIV-related disorder.

**[0128]** The ability of the test compound to modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding to a substrate or to bind to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can also be determined. Determining the ability of the test compound to modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding to a substrate can be accomplished, for example, by coupling the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate with a radioisotope or enzymatic label such that binding of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be determined by

detecting the labeled 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate in a complex. 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 could also be coupled with a radioisotope or enzymatic label to monitor the ability of a test compound to modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate in a complex. Determining the ability of the test compound to bind 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be determined by detecting the labeled 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 compound in a complex. For example, compounds (*e.g.*, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 ligands or substrates) can be labeled with  $^{125}\text{I}$ ,  $^{35}\text{S}$ ,  $^{14}\text{C}$ , or  $^3\text{H}$ , either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Compounds can further be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

**[0129]** It is also within the scope of this invention to determine the ability of a compound (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 ligand or substrate) to interact with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 without the labeling of any of



the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 without the labeling of either the compound or the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 (McConnell, H. M. *et al.* (1992) *Science* 257:1906-1912. As used herein, a "microphysiometer" (*e.g.*, Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777.

[0130] In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate) with a test compound and determining the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule. Determining the ability of the test compound to modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule can be accomplished, for example, by determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to bind to or interact with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule.

[0131] Determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or a biologically active fragment

thereof, to bind to or interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule can be accomplished by one of the methods described above for determining direct binding. In a preferred embodiment, determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to bind to or interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.*, intracellular  $\text{Ca}^{2+}$ , diacylglycerol,  $\text{IP}_3$ , cAMP), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a target-regulated cellular response (*e.g.*, gene expression).

[0132] In yet another embodiment, an assay of the present invention is a cell-free assay in which a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof, is contacted with a test compound and the ability of the test compound to bind to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof is determined. Preferred biologically active portions of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins to be used in assays of the present invention include fragments which participate in interactions with non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 molecules, *e.g.*, fragments with high surface probability scores. Binding of the test compound to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting

the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof with a known compound which binds 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, wherein determining the ability of the test compound to interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein comprises determining the ability of the test compound to preferentially bind to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 or biologically active portion thereof as compared to the known compound. Compounds that modulate the interaction of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 with a known target protein may be useful in regulating the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, especially a mutant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

[0133] In another embodiment, the assay is a cell-free assay in which a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822,

33945, 43748, 47161, 81982 or 46777 protein can be accomplished, for example, by determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to bind to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule by one of the methods described above for determining direct binding. Determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to bind to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA) (Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345 and Szabo *et al.* (1995) *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

[0134] In another embodiment, determining the ability of the test compound to modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be accomplished by determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to further modulate the activity of a downstream effector of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule. For example, the activity of the effector molecule on an appropriate target can be determined or the binding of the effector to an appropriate target can be determined as previously described.

[0135] In yet another embodiment, the cell-free assay involves contacting a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof with a known compound which binds the

9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, wherein determining the ability of the test compound to interact with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein comprises determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to preferentially bind to or modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule.

**[0136]** In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, or interaction of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or

glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, and the mixture incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding or activity determined using standard techniques.

[0137] Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or target molecules but which do not interfere with binding of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to its target molecule can be derivatized to the wells of the plate, and unbound target or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above

for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or target molecule.

[0138] In another embodiment, modulators of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein in the cell is determined. The level of expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein in the presence of the candidate compound is compared to the level of expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression based on this comparison. For example, when expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein expression. Alternatively, when expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of

9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein expression. The level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein expression in the cells can be determined by methods described herein for detecting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein.

[0139] In yet another aspect of the invention, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J. Biol. Chem.* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300), to identify other proteins, which bind to or interact with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 ("9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -binding proteins" or "9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -bp") and are involved in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. Such 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -binding proteins are also likely to be involved in the propagation of signals by the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 targets as, for example, downstream elements of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -mediated signaling



pathway. Alternatively, such 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -binding proteins are likely to be 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 inhibitors.

**[0140]** The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

**[0141]** In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be confirmed *in vivo*, *e.g.*, in an animal such as an animal model for AIDS or an HIV-related disorder, as described herein.

**[0142]** This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further

use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulating agent, an antisense 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecule, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -specific antibody, or a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

[0143] Any of the compounds, including but not limited to compounds such as those identified in the foregoing assay systems, may be tested for the ability to ameliorate at least one symptom of AIDS or an HIV-related disorder. Cell-based and animal model-based assays for the identification of compounds exhibiting such an ability to ameliorate at least one symptom of AIDS or an HIV-related disorder are described herein.

[0144] In addition, animal-based models of AIDS or an HIV-related disorder, such as those described herein, may be used to identify compounds capable of treating AIDS or an HIV-related disorder. Such animal models may be used as test substrates for the identification of drugs, pharmaceuticals, therapies, and interventions which may be effective in treating AIDS or an HIV-related disorder. For example, animal models may be exposed to a compound, suspected of exhibiting an ability to treat AIDS or an HIV-related disorder, at a sufficient concentration and for a time sufficient to elicit such an amelioration of at least one symptom of AIDS or an HIV-related disorder in the exposed animals. The response of the animals to the exposure may be monitored by assessing the reversal of the symptoms of AIDS or an HIV-related disorder before and after treatment.

[0145] With regard to intervention, any treatments which reverse any aspect of a viral disorder (*i.e.* have an effect on AIDS or an HIV-related disorder) should be

considered as candidates for AIDS or an HIV-related disorder therapeutic intervention.

Dosages of test agents may be determined by deriving dose-response curves.

[0146] Additionally, gene expression patterns may be utilized to assess the ability of a compound to ameliorate at least one symptom of AIDS or an HIV-related disorder. For example, the expression pattern of one or more genes may form part of a "gene expression profile" or "transcriptional profile" which may be then be used in such an assessment. "Gene expression profile" or "transcriptional profile", as used herein, includes the pattern of mRNA expression obtained for a given tissue or cell type under a given set of conditions. Gene expression profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR. In one embodiment, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences may be used as probes and/or PCR primers for the generation and corroboration of such gene expression profiles.

[0147] Gene expression profiles may be characterized for known states, either viral disease or normal, within the cell- and/or animal-based model systems. Subsequently, these known gene expression profiles may be compared to ascertain the effect a test compound has to modify such gene expression profiles, and to cause the profile to more closely resemble that of a more desirable profile.

[0148] For example, administration of a compound may cause the gene expression profile of AIDS or an HIV-related disorder disease model system to more closely resemble the control system. Administration of a compound may, alternatively, cause the gene expression profile of a control system to begin to mimic AIDS or an HIV-related disorder or AIDS or an HIV-related disease state. Such a compound may, for example, be used in further characterizing the compound of interest, or may be used in the generation of additional animal models.

## II. Cell- and Animal-Based Model Systems

[0149] Described herein are cell- and animal-based systems which act as models for AIDS or an HIV-related disorder. These systems may be used in a variety of applications. For example, the cell- and animal-based model systems may be used to further characterize differentially expressed genes associated with AIDS or an HIV-related disorder, *e.g.*, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777. In addition, animal- and cell-based assays may be used as part of screening strategies designed to identify compounds which are capable of ameliorating at least one symptom of AIDS or an HIV-related disorder, as described, below. Thus, the animal- and cell-based models may be used to identify drugs, pharmaceuticals, therapies and interventions which may be effective in treating AIDS or an HIV-related disorder. Furthermore, such animal models may be used to determine the LD50 and the ED50 in animal subjects, and such data can be used to determine the *in vivo* efficacy of potential urological disorder treatments.

### A. Animal-Based Systems

[0150] Animal-based model systems of urological disorder may include, but are not limited to, non-recombinant and engineered transgenic animals.

[0151] Non-recombinant animal models for AIDS or an HIV-related disorder may include, for example, genetic models.

[0152] Additionally, animal models exhibiting AIDS or an HIV-related disorder may be engineered by using, for example, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences described above, in conjunction with techniques for producing transgenic animals that are well known to those of skill in the art. For example, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences may be introduced into, and overexpressed in, the genome of the animal of interest, or, if endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences are present, they may either be overexpressed or, alternatively, be disrupted in order to underexpress or inactivate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865,

12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression.

[0153] The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -coding sequences have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences have been introduced into their genome or homologous recombinant animals in which endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences have been altered. Such animals are useful for studying the function and/or activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 and for identifying and/or evaluating modulators of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, and the like. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, e.g., an embryonic cell of the animal, prior to development of the animal.

[0154] A transgenic animal used in the methods of the invention can be created by introducing a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -encoding nucleic acid into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 cDNA sequence can be introduced as a transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of a human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, such as a mouse or rat 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, can be used as a transgene. Alternatively, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene homologue, such as another 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 family member, can be isolated based on hybridization to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 cDNA sequences and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 transgene to direct expression of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods

are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 transgene in its genome and/or expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can further be bred to other transgenic animals carrying other transgenes.

[0155] To create a homologous recombinant animal, a vector is prepared which contains at least a portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene. The 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene can be a human gene but more preferably, is a non-human homologue of a human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene. For example, a rat 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene can be used to construct a homologous recombination nucleic acid molecule, *e.g.*, a vector, suitable for altering an endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene in the mouse genome. In a preferred embodiment, the homologous recombination nucleic acid molecule is designed such that, upon homologous recombination, the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene is functionally disrupted

(i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the homologous recombination nucleic acid molecule can be designed such that, upon homologous recombination, the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby alter the expression of the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein). In the homologous recombination nucleic acid molecule, the altered portion of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene is flanked at its 5' and 3' ends by additional nucleic acid sequence of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene to allow for homologous recombination to occur between the exogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene carried by the homologous recombination nucleic acid molecule and an endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene in a cell, e.g., an embryonic stem cell. The additional flanking 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid sequence is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the homologous recombination nucleic acid molecule (see, e.g., Thomas, K.R. and Capecchi, M. R. (1987) *Cell* 51:503 for a description of homologous recombination vectors). The homologous recombination nucleic acid molecule is introduced into a cell, e.g., an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene has homologously recombined with the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748,



47161, 81982 or 46777 gene are selected (see *e.g.*, Li, E. *et al.* (1992) *Cell* 69:915). The selected cells can then be injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see *e.g.*, Bradley, A. in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E.J. Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination nucleic acid molecules, *e.g.*, vectors, or homologous recombinant animals are described further in Bradley, A. (1991) *Current Opinion in Biotechnology* 2:823-829 and in PCT International Publication Nos.: WO 90/11354 by Le Mouellec *et al.*; WO 91/01140 by Smithies *et al.*; WO 92/0968 by Zijlstra *et al.*; and WO 93/04169 by Berns *et al.*

[0156] In another embodiment, transgenic non-human animals for use in the methods of the invention can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.* (1991) *Science* 251:1351-1355). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

[0157] Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al.* (1997) *Nature* 385:810-813 and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, *e.g.*, a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G<sub>0</sub> phase. The quiescent cell can then be fused, *e.g.*, through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster

animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell, *e.g.*, the somatic cell, is isolated.

[0158] The 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 transgenic animals that express 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 peptide (detected immunocytochemically, using antibodies directed against 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 epitopes) at easily detectable levels should then be further evaluated to identify those animals which display a characteristic HIV-related disorder.

#### B. Cell-Based Systems

[0159] Cells that contain and express 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences which encode a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, and, further, exhibit cellular phenotypes associated AIDS or an HIV-related disorder, may be used to identify compounds that exhibit an effect on AIDS or an HIV-related disorder. Such cells may include non-recombinant monocyte cell lines, such as U937 (ATCC# CRL-1593), THP-1 (ATCC#TIB-202), and P388D1 (ATCC# TIB-63); endothelial cells such as human umbilical vein endothelial cells (HUVECs), human microvascular endothelial cells (HMVEC), and bovine aortic endothelial cells (BAECs); as well as generic mammalian cell lines such as HeLa cells and COS cells, *e.g.*, COS-7 (ATCC# CRL-1651), and T-cell or monocyte cell lines.. Further, such cells may include recombinant, transgenic cell lines. For example, the AIDS or an HIV-related disorder animal models of the invention, discussed above, may be used to generate cell lines, containing one or more cell types involved in AIDS or an HIV-related disorder, that can be used as cell culture models for this disorder. While primary cultures derived from the urological disorder model transgenic animals of the invention may be utilized, the generation of continuous cell lines

is preferred. For examples of techniques which may be used to derive a continuous cell line from the transgenic animals, see Small *et al.*, (1985) *Mol. Cell Biol.* 5:642-648.

[0160] Alternatively, cells of a cell type known to be involved in AIDS or an HIV-related disorder may be transfected with sequences capable of increasing or decreasing the amount of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression within the cell. For example, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences may be introduced into, and overexpressed in, the genome of the cell of interest, or, if endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences are present, they may be either overexpressed or, alternatively disrupted in order to underexpress or inactivate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression.

[0161] In order to overexpress a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, the coding portion of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene may be ligated to a regulatory sequence which is capable of driving gene expression in the cell type of interest, *e.g.*, an endothelial cell. Such regulatory regions will be well known to those of skill in the art, and may be utilized in the absence of undue experimentation.

Recombinant methods for expressing target genes are described above.

[0162] For underexpression of an endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequence, such a sequence may be isolated and engineered such that when reintroduced into the genome of the cell type of interest, the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 alleles will be inactivated. Preferably, the engineered 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence

is introduced via gene targeting such that the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence is disrupted upon integration of the engineered 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence into the cell's genome. Transfection of host cells with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 genes is discussed, above.

[0163] Cells treated with compounds or transfected with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 genes can be examined for phenotypes associated with AIDS or an HIV-related disorder.

[0164] Transfection of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid may be accomplished by using standard techniques (described in, for example, Ausubel (1989) *supra*). Transfected cells should be evaluated for the presence of the recombinant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences, for expression and accumulation of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA, and for the presence of recombinant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein production. In instances wherein a decrease in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression is desired, standard techniques may be used to demonstrate whether a decrease in endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression and/or in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein production is achieved.

[0165] Also provided are cells or a purified preparation thereof, e.g., human cells, in which an endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 is under the control of a regulatory sequence that does not normally control the expression of the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene. The expression characteristics of an endogenous gene within a cell, e.g., a cell line or microorganism, can be modified by inserting a heterologous DNA regulatory element into the genome of the cell such that the inserted regulatory element is operably linked to the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene. For example, an endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, e.g., a gene which is "transcriptionally silent," e.g., not normally expressed, or expressed only at very low levels, may be activated by inserting a regulatory element which is capable of promoting the expression of a normally expressed gene product in that cell. Techniques such as targeted homologous recombinations, can be used to insert the heterologous DNA as described in, e.g., Chappel, US 5,272,071; WO 91/06667, published on May 16, 1991.

### III. Predictive Medicine:

[0166] The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein and/or nucleic acid expression as well as 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077,

1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity, in the context of a biological sample (*e.g.*, blood, serum, cells, *e.g.*, endothelial cells, or tissue, *e.g.*, vascular tissue, lymphoid tissue, peripheral blood cells) to thereby determine whether an individual is afflicted with a predisposition or is experiencing AIDS or an HIV-related disorder. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing AIDS or an HIV-related disorder. For example, mutations in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene can be assayed for in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of AIDS or an HIV-related disorder.

[0167] Another aspect of the invention pertains to monitoring the influence of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulators (*e.g.*, anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 ribozymes) on the expression or activity of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 in clinical trials.

[0168] These and other agents are described in further detail in the following sections.

#### A. Diagnostic Assays

[0169] To determine whether a subject is afflicted with a disease, a biological sample may be obtained from a subject and the biological sample may be contacted with a compound or an agent capable of detecting a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or nucleic acid (*e.g.*, mRNA or genomic DNA) that encodes a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, in the biological sample. A preferred agent for

detecting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or genomic DNA. The nucleic acid probe can be, for example, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid set forth in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, or a portion thereof, such as an oligonucleotide of at least 15, 20, 25, 30, 35, 40, 45, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

[0170] A preferred agent for detecting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein in a sample is an antibody capable of binding to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')<sub>2</sub>) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

[0171] The term "biological sample" is intended to include tissues, cells, and biological fluids isolated from a subject, as well as tissues, cells, and fluids present within a subject. That is, the detection method of the invention can be used to detect 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA,

protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein include introducing into a subject a labeled anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

[0172] In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA, or genomic DNA, such that the presence of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA or genomic DNA in the control sample with the presence of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA or genomic DNA in the test sample.



B. Prognostic Assays

[0173] The present invention further pertains to methods for identifying subjects having or at risk of developing a disease associated with aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity.

[0174] As used herein, the term "aberrant" includes a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity which deviates from the wild type 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity. Aberrant expression or activity includes increased or decreased expression or activity, as well as expression or activity which does not follow the wild type developmental pattern of expression or the subcellular pattern of expression. For example, aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity is intended to include the cases in which a mutation in the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene causes the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene to be under-expressed or over-expressed and situations in which such mutations result in a non-functional 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or a protein which does not function in a wild-type fashion, *e.g.*, a protein which does not interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate, or one which interacts with a non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate.

[0175] The assays described herein, such as the preceding diagnostic assays or the following assays, can be used to identify a subject having or at risk of developing a disease. A biological sample may be obtained from a subject and tested for the presence or absence of a genetic alteration. For example, such genetic alterations can be detected by

ascertaining the existence of at least one of 1) a deletion of one or more nucleotides from a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 2) an addition of one or more nucleotides to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 3) a substitution of one or more nucleotides of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 4) a chromosomal rearrangement of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 5) an alteration in the level of a messenger RNA transcript of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 6) aberrant modification of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, such as of the methylation pattern of the genomic DNA, 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 8) a non-wild type level of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -protein, 9) allelic loss of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, and 10) inappropriate post-translational modification of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -protein.

**[0176]** As described herein, there are a large number of assays known in the art which can be used for detecting genetic alterations in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene. For example, a genetic alteration in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161,

81982 or 46777 gene may be detected using a probe/primer in a polymerase chain reaction (PCR) (see, *e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, *e.g.*, Landegran *et al.* (1988) *Science* 241:1077-1080; and Nakazawa *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for detecting point mutations in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene (see Abravaya *et al.* (1995) *Nucleic Acids Res.* 23:675-682). This method includes collecting a biological sample from a subject, isolating nucleic acid (*e.g.*, genomic DNA, mRNA or both) from the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene under conditions such that hybridization and amplification of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

[0177] Alternative amplification methods include: self sustained sequence replication (Guatelli, J.C. *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh, D.Y. *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi, P.M. *et al.* (1988) *Bio-Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

[0178] In an alternative embodiment, mutations in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene from a biological sample can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis

and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (see, for example, U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

[0179] In other embodiments, genetic mutations in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be identified by hybridizing biological sample derived and control nucleic acids, *e.g.*, DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotide probes (Cronin, M.T. *et al.* (1996) *Human Mutation* 7:244-255; Kozal, M.J. *et al.* (1996) *Nature Medicine* 2:753-759). For example, genetic mutations in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, M.T. *et al.* (1996) *supra*. Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential, overlapping probes. This step allows for the identification of point mutations. This step is followed by a second hybridization array that allows for the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

[0180] In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene in a biological sample and detect mutations by comparing the sequence of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 in the biological sample with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxam and Gilbert (1977) *Proc. Natl. Acad. Sci. USA* 74:560) or Sanger (1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays (Naeve, C. W. (1995) *Biotechniques* 19:448-53),

including sequencing by mass spectrometry (see, e.g., PCT International Publication No. WO 94/16101; Cohen *et al.* (1996) *Adv. Chromatogr.* 36:127-162; and Griffin *et al.* (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

[0181] Other methods for detecting mutations in the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers *et al.* (1985) *Science* 230:1242). In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes formed by hybridizing (labeled) RNA or DNA containing the wild-type 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S1 nuclease to enzymatically digest the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. See, for example, Cotton *et al.* (1988) *Proc. Natl Acad Sci USA* 85:4397 and Saleeba *et al.* (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.

[0182] In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu *et al.* (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735,

1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence, *e.g.*, a wild-type 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. See, for example, U.S. Patent No. 5,459,039.

**[0183]** In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita *et al.* (1989) *Proc Natl. Acad. Sci USA*: 86:2766; see also Cotton (1993) *Mutat. Res.* 285:125-144 and Hayashi (1992) *Genet. Anal. Tech. Appl.* 9:73-79). Single-stranded DNA fragments of sample and control 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen *et al.* (1991) *Trends Genet* 7:5).

**[0184]** In yet another embodiment the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers *et al.* (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to ensure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys Chem* 265:12753).

[0185] Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki *et al.* (1986) *Nature* 324:163); Saiki *et al.* (1989) *Proc. Natl Acad. Sci USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

[0186] Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs *et al.* (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini *et al.* (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

[0187] Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, or small molecule) to effectively treat a disease.

#### C. Monitoring of Effects During Clinical Trials

[0188] The present invention further provides methods for determining the effectiveness of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748,

47161, 81982 or 46777 modulator (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator identified herein) in treating a disease. For example, the effectiveness of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator in increasing 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression, protein levels, or in upregulating 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity, can be monitored in clinical trials of subjects exhibiting decreased 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression, protein levels, or downregulated 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity.

Alternatively, the effectiveness of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator in decreasing 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression, protein levels, or in downregulating 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity, can be monitored in clinical trials of subjects exhibiting increased 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression, protein levels, or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. In such clinical trials, the expression or activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, and preferably, other genes that have been implicated in nociception can be used as a "read out" or marker of the phenotype of a particular cell.



[0189] For example, and not by way of limitation, genes, including 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777, that are modulated in cells by treatment with an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity (*e.g.*, identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents which modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity on subjects suffering from AIDS or an HIV-related disorder in, for example, a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 and other genes implicated in the HIV-related disorder. The levels of gene expression (*e.g.*, a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods described herein, or by measuring the levels of activity of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 or other genes. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. This response state may be determined before, and at various points during treatment of the individual with the agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity.

[0190] In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, or small molecule identified by the screening assays described herein) including the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the

agent; (ii) detecting the level of expression of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA, or genomic DNA in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA, or genomic DNA in the pre-administration sample with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 to lower levels than detected, *i.e.* to decrease the effectiveness of the agent. According to such an embodiment, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity may be used as an indicator of the effectiveness of an agent, even in the absence of an observable phenotypic response.

#### IV. Methods of Treatment:

[0191] The present invention provides for both prophylactic and therapeutic methods of treating a subject, *e.g.*, a human, at risk of (or susceptible to) a disease. With regard to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored or modified, based on knowledge obtained from the field of

pharmacogenomics. "Pharmacogenomics," as used herein, refers to the application of genomics technologies such as gene sequencing, statistical genetics, and gene expression analysis to drugs in clinical development and on the market. More specifically, the term refers to the study of how a patient's genes determine his or her response to a drug (*e.g.*, a patient's "drug response phenotype", or "drug response genotype").

[0192] Thus, another aspect of the invention provides methods for tailoring an subject's prophylactic or therapeutic treatment with either the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 molecules of the present invention or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulators according to that individual's drug response genotype. Pharmacogenomics allows a clinician or physician to target prophylactic or therapeutic treatments to patients who will most benefit from the treatment and to avoid treatment of patients who will experience toxic drug-related side effects.

A. Prophylactic Methods

[0193] In one aspect, the invention provides a method for preventing in a subject, a disease by administering to the subject an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. Subjects at risk for AIDS or an HIV-related disorder, *e.g.*, can be identified by, for example, any or a combination of the diagnostic or prognostic assays described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity, such that a disease is prevented or, alternatively, delayed in its progression. Depending on the type of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 aberrancy, for example, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or

46777 agonist or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

#### B. Therapeutic Methods

[0194] Described herein are methods and compositions whereby AIDS or an HIV-related disorder may be ameliorated. Certain urological disorders are brought about, at least in part, by an excessive level of a gene product, or by the presence of a gene product exhibiting an abnormal or excessive activity. As such, the reduction in the level and/or activity of such gene products would bring about the amelioration of at least one symptom of AIDS or an HIV-related disorder. Techniques for the reduction of gene expression levels or the activity of a protein are discussed below.

[0195] Alternatively, certain other HIV-related disorders are brought about, at least in part, by the absence or reduction of the level of gene expression, or a reduction in the level of a protein's activity. As such, an increase in the level of gene expression and/or the activity of such proteins would bring about the amelioration of at least one symptom of AIDS or an HIV-related disorder.

[0196] In some cases, the up-regulation of a gene in a disease state reflects a protective role for that gene product in responding to the disease condition. Enhancement of such a gene's expression, or the activity of the gene product, will reinforce the protective effect it exerts. Some urological disease states may result from an abnormally low level of activity of such a protective gene. In these cases also, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of at least one symptom of AIDS or an HIV-related disorder. Techniques for increasing target gene expression levels or target gene product activity levels are discussed herein.

[0197] Accordingly, another aspect of the invention pertains to methods of modulating 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the modulatory method of the invention involves contacting a cell with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 or agent that modulates one or more of the activities of 9145, 1725, 311, 837,

58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein activity associated with the cell (*e.g.*, an endothelial cell, ovarian cell, T-cell or monocyte). An agent that modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring target molecule of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777, ligand or substrate), a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 agonist or antagonist, a peptidomimetic of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 agonist or antagonist, or other small molecule. In one embodiment, the agent stimulates one or more 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activities. Examples of such stimulatory agents include active 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein and a nucleic acid molecule encoding 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 that has been introduced into the cell. In another embodiment, the agent inhibits one or more 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activities. Examples of such inhibitory agents include antisense 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules, anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786,

10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies, and 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 inhibitors. These modulatory methods can be performed *in vitro* (e.g., by culturing the cell with the agent) or, alternatively, *in vivo* (e.g., by administering the agent to a subject). As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant or unwanted expression or activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (e.g., an agent identified by a screening assay described herein), or combination of agents that modulates (e.g., upregulates or downregulates) 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity. In another embodiment, the method involves administering a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity.

**[0198]** Stimulation of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is desirable in situations in which 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 is abnormally downregulated and/or in which increased 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is likely to have a beneficial effect.

Likewise, inhibition of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is desirable in situations in which 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 is abnormally upregulated and/or in which decreased 9145, 1725, 311, 837, 58305, 156, 14175, 50352,

32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is likely to have a beneficial effect.

(i) Methods for Inhibiting Target Gene Expression, Synthesis, or Activity

[0199] As discussed above, genes involved in viral disorders may cause such disorders via an increased level of gene activity. In some cases, such up-regulation may have a causative or exacerbating effect on the disease state. A variety of techniques may be used to inhibit the expression, synthesis, or activity of such genes and/or proteins.

[0200] For example, compounds such as those identified through assays described above, which exhibit inhibitory activity, may be used in accordance with the invention to ameliorate at least one symptom of AIDS or an HIV-related disorder. Such molecules may include, but are not limited to, small organic molecules, peptides, antibodies, and the like.

[0201] For example, compounds can be administered that compete with endogenous ligand for the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. The resulting reduction in the amount of ligand-bound 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein will modulate endothelial cell physiology. Compounds that can be particularly useful for this purpose include, for example, soluble proteins or peptides, such as peptides comprising one or more of the extracellular domains, or portions and/or analogs thereof, of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, including, for example, soluble fusion proteins such as Ig-tailed fusion proteins. (For a discussion of the production of Ig-tailed fusion proteins, see, for example, U.S. Pat. No. 5,116,964). Alternatively, compounds, such as ligand analogs or antibodies, that bind to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 receptor site, but do not activate the protein, (*e.g.*, receptor-ligand antagonists) can be effective in inhibiting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein activity.

[0202] Further, antisense and ribozyme molecules which inhibit expression of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397,

13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene may also be used in accordance with the invention to inhibit aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene activity. Still further, triple helix molecules may be utilized in inhibiting aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene activity.

[0203] The antisense nucleic acid molecules used in the methods of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention include direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

[0204] In yet another embodiment, an antisense nucleic acid molecule used in the methods of the invention is an  $\alpha$ -anomeric nucleic acid molecule. An  $\alpha$ -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\beta$ -units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids. Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise



a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.* (1987) *FEBS Lett.* 215:327-330).

[0205] In still another embodiment, an antisense nucleic acid used in the methods of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA transcripts to thereby inhibit translation of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA. A ribozyme having specificity for a 34021, 1720, 1683, 1552, 1682, 1675, 12825, 9952, 5816, 10002 or 1611-encoding nucleic acid can be designed based upon the nucleotide sequence of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 cDNA disclosed herein (*i.e.*, SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a 34021, 1720, 1683, 1552, 1682, 1675, 12825, 9952, 5816, 10002 or 1611-encoding mRNA (see, for example, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742). Alternatively, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, for example, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418).

[0206] 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression can also be inhibited by targeting nucleotide sequences complementary to the regulatory region of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 (*e.g.*, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786,

10220, 17822, 33945, 43748, 47161, 81982 or 46777 promoter and/or enhancers) to form triple helical structures that prevent transcription of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene in target cells (see, for example, Helene, C. (1991) *Anticancer Drug Des.* 6(6):569-84; Helene, C. *et al.* (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher, L.J. (1992) *Bioassays* 14(12):807-15).

**[0207]** Antibodies that are both specific for the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein and interfere with its activity may also be used to modulate or inhibit 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein function. Such antibodies may be generated using standard techniques described herein, against the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein itself or against peptides corresponding to portions of the protein. Such antibodies include but are not limited to polyclonal, monoclonal, Fab fragments, single chain antibodies, or chimeric antibodies.

**[0208]** In instances where the target gene protein is intracellular and whole antibodies are used, internalizing antibodies may be preferred. Lipofectin liposomes may be used to deliver the antibody or a fragment of the Fab region which binds to the target epitope into cells. Where fragments of the antibody are used, the smallest inhibitory fragment which binds to the target protein's binding domain is preferred. For example, peptides having an amino acid sequence corresponding to the domain of the variable region of the antibody that binds to the target gene protein may be used. Such peptides may be synthesized chemically or produced via recombinant DNA technology using methods well known in the art (described in, for example, Creighton (1983), *supra*; and Sambrook *et al.* (1989) *supra*). Single chain neutralizing antibodies which bind to intracellular target gene epitopes may also be administered. Such single chain antibodies may be administered, for example, by expressing nucleotide sequences encoding single-chain antibodies within the target cell population by utilizing, for example, techniques such as those described in Marasco *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:7889-7893).

**[0209]** In some instances, the target gene protein is extracellular, or is a transmembrane protein, such as the 9145, 1725, 311, 837, 58305, 156, 14175, 50352,

32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Antibodies that are specific for one or more extracellular domains of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, for example, and that interfere with its activity, are particularly useful in treating AIDS or an HIV-related disorder. Such antibodies are especially efficient because they can access the target domains directly from the bloodstream. Any of the administration techniques described below which are appropriate for peptide administration may be utilized to effectively administer inhibitory target gene antibodies to their site of action.

(ii) Methods for Restoring or Enhancing Target Gene Activity

[0210] Genes that cause AIDS or an HIV-related disorder may be underexpressed within BPH and/or UI. Alternatively, the activity of the protein products of such genes may be decreased, leading to the development of AIDS or an HIV-related disorder. Such down-regulation of gene expression or decrease of protein activity might have a causative or exacerbating effect on the disease state.

[0211] In some cases, genes that are up-regulated in the disease state might be exerting a protective effect. A variety of techniques may be used to increase the expression, synthesis, or activity of genes and/or proteins that exert a protective effect in response to AIDS or an HIV-related disorder.

[0212] Described in this section are methods whereby the level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity may be increased to levels wherein the symptoms of the HIV-related disorder are ameliorated. The level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity may be increased, for example, by either increasing the level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression or by increasing the level of active 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein which is present.

[0213] For example, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, at a level sufficient to ameliorate at least one symptom of AIDS or an HIV-related disorder may be administered to a patient exhibiting such symptoms. Any of the techniques discussed below may be used for such administration. One of skill in the art will readily know how to determine the concentration of effective, non-toxic doses of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, utilizing techniques such as those described below.

[0214] Additionally, RNA sequences encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein may be directly administered to a patient exhibiting AIDS or an HIV-related disorder, at a concentration sufficient to produce a level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein such that AIDS or an HIV-related disorder are ameliorated. Any of the techniques discussed below, which achieve intracellular administration of compounds, such as, for example, liposome administration, may be used for the administration of such RNA molecules. The RNA molecules may be produced, for example, by recombinant techniques such as those described herein.

[0215] Further, subjects may be treated by gene replacement therapy. One or more copies of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, or a portion thereof, that directs the production of a normal 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 function, may be inserted into cells using vectors which include, but are not limited to adenovirus, adeno-associated virus, and retrovirus vectors, in addition to other particles that introduce DNA into cells, such as liposomes. Additionally, techniques such as those described above may be used for the introduction of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077,

1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences into human cells.

[0216] Cells, preferably, autologous cells, containing 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expressing gene sequences may then be introduced or reintroduced into the subject at positions which allow for the amelioration of at least one symptom of AIDS or an HIV-related disorder. Such cell replacement techniques may be preferred, for example, when the gene product is a secreted, extracellular gene product.

### C. Pharmaceutical Compositions

[0217] Another aspect of the invention pertains to methods for treating a subject suffering from a disease. These methods involve administering to a subject an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity (e.g., an agent identified by a screening assay described herein), or a combination of such agents. In another embodiment, the method involves administering to a subject a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity.

[0218] Stimulation of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is desirable in situations in which 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 is abnormally downregulated and/or in which increased 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is likely to have a beneficial effect. Likewise, inhibition of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is desirable in situations in which 9145, 1725, 311, 837,

58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 is abnormally upregulated and/or in which decreased 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is likely to have a beneficial effect.

[0219] The agents which modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity can be administered to a subject using pharmaceutical compositions suitable for such administration. Such compositions typically comprise the agent (*e.g.*, nucleic acid molecule, protein, or antibody) and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0220] A pharmaceutical composition used in the therapeutic methods of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0221] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the

extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0222] Sterile injectable solutions can be prepared by incorporating the agent that modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity (*e.g.*, a fragment of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or an anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220; 17822, 33945, 43748, 47161, 81982 or 46777 antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0223] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0224] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0225] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0226] The agents that modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0227] In one embodiment, the agents that modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery



systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

[0228] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the agent that modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an agent for the treatment of subjects.

[0229] Toxicity and therapeutic efficacy of such agents can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and can be expressed as the ratio LD<sub>50</sub>/ED<sub>50</sub>. Agents which exhibit large therapeutic indices are preferred. While agents that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such agents to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[0230] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulating agents lies preferably within a range of circulating concentrations that include the ED<sub>50</sub> with little or no toxicity. The dosage may vary within this range depending upon

the dosage form employed and the route of administration utilized. For any agent used in the therapeutic methods of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC<sub>50</sub> (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[0231] As defined herein, a therapeutically effective amount of protein or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

[0232] In a preferred example, a subject is treated with antibody, protein, or polypeptide in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody, protein, or polypeptide used for treatment may increase or decrease over the course of a particular treatment. Changes in dosage may result and become apparent from the results of diagnostic assays as described herein.

[0233] The present invention encompasses agents which modulate expression or activity. An agent may, for example, be a small molecule. For example, such small molecules include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (*i.e.*, including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams

per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds. It is understood that appropriate doses of small molecule agents depends upon a number of factors within the ken of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of the small molecule will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the small molecule to have upon the nucleic acid or polypeptide of the invention.

[0234] Exemplary doses include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (*e.g.*, about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). It is

[0235] furthermore understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. Such appropriate doses may be determined using the assays described herein. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

[0236] Further, an antibody (or fragment thereof) may be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not

limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

[0237] The conjugates of the invention can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[0238] Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982). Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

[0239] The nucleic acid molecules used in the methods of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be

delivered to a subject by, for example, intravenous injection, local administration (see U.S. Patent 5,328,470) or by stereotactic injection (see, *e.g.*, Chen *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

#### D. Pharmacogenomics

[0240] In conjunction with the therapeutic methods of the invention, pharmacogenomics (*i.e.*, the study of the relationship between a subject's genotype and that subject's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity, as well as tailoring the dosage and/or therapeutic regimen of treatment with an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity.

[0241] Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, for example, Eichelbaum, M. *et al.* (1996) *Clin. Exp. Pharmacol. Physiol.* 23(10-11): 983-985 and Linder, M.W. *et al.* (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare genetic defects or as naturally-occurring polymorphisms. For example,

glucose-6-phosphate aminopeptidase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

[0242] One pharmacogenomics approach to identifying genes that predict drug response, known as "a genome-wide association", relies primarily on a high-resolution map of the human genome consisting of already known gene-related markers (*e.g.*, a "bi-allelic" gene marker map which consists of 60,000-100,000 polymorphic or variable sites on the human genome, each of which has two variants). Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, such a high resolution map can be generated from a combination of some ten million known single nucleotide polymorphisms (SNPs) in the human genome. As used herein, a "SNP" is a common alteration that occurs in a single nucleotide base in a stretch of DNA. For example, a SNP may occur once per every 1000 bases of DNA. A SNP may be involved in a disease process, however, the vast majority may not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that may be common among such genetically similar individuals.

[0243] Alternatively, a method termed the "candidate gene approach" can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drug target is known (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein used in the methods of the present invention), all common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

[0244] As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and the cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug

response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

[0245] Alternatively, a method termed the "gene expression profiling" can be utilized to identify genes that predict drug response. For example, the gene expression of an animal dosed with a drug (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 molecule or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator used in the methods of the present invention) can give an indication whether gene pathways related to toxicity have been turned on.

[0246] Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment of a subject. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and, thus, enhance therapeutic or prophylactic efficiency when treating a subject suffering from AIDS or an HIV-related disorder, with an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity.

#### V. Recombinant Expression Vectors and Host Cells Used in the Methods of the Invention

[0247] The methods of the invention (*e.g.*, the screening assays described herein) include the use of vectors, preferably expression vectors, containing a nucleic acid

encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

[0248] The recombinant expression vectors to be used in the methods of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operatively linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel (1990) *Methods Enzymol.* 185:3-7. Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cells and those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be



appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (*e.g.*, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins, mutant forms of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins, fusion proteins, and the like).

[0249] The recombinant expression vectors to be used in the methods of the invention can be designed for expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins in prokaryotic or eukaryotic cells. For example, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins can be expressed in bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells, or mammalian cells. Suitable host cells are discussed further in Goeddel (1990) *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

[0250] Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith, D.B. and Johnson, K.S. (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and

pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

[0251] Purified fusion proteins can be utilized in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity assays, (*e.g.*, direct assays or competitive assays described in detail below), or to generate antibodies specific for 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins. In a preferred embodiment, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion protein expressed in a retroviral expression vector of the present invention can be utilized to infect bone marrow cells which are subsequently transplanted into irradiated recipients. The pathology of the subject recipient is then examined after sufficient time has passed (*e.g.*, six weeks).

[0252] In another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, B. (1987) *Nature* 329:840) and pMT2PC (Kaufman *et al.* (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook, J. *et al.*, *Molecular Cloning: A Laboratory Manual. 2nd ed.*, Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

[0253] In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid).

[0254] The methods of the invention may further use a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA. Regulatory sequences operatively

linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific, or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes, see Weintraub, H. *et al.*, Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) 1986.

[0255] Another aspect of the invention pertains to the use of host cells into which a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecule of the invention is introduced, *e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecule within a recombinant expression vector or a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecule containing sequences which allow it to homologously recombine into a specific site of the host cell's genome. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[0256] A host cell can be any prokaryotic or eukaryotic cell. For example, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

[0257] Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms

"transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook *et al.* (*Molecular Cloning: A Laboratory Manual*, 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), and other laboratory manuals.

[0258] A host cell used in the methods of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Accordingly, the invention further provides methods for producing a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein has been introduced) in a suitable medium such that a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein is produced. In another embodiment, the method further comprises isolating a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein from the medium or the host cell.

#### VI. Isolated Nucleic Acid Molecules Used in the Methods of the Invention

[0259] The methods of the invention include the use of isolated nucleic acid molecules that encode 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins or biologically active portions thereof, as well as nucleic acid fragments sufficient for use as hybridization probes to identify 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -encoding nucleic acid

molecules (e.g., 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA) and fragments for use as PCR primers for the amplification or mutation of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (e.g., cDNA or genomic DNA) and RNA molecules (e.g., mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

[0260] A nucleic acid molecule used in the methods of the present invention, e.g., a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, as a hybridization probe, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

[0261] Moreover, a nucleic acid molecule encompassing all or a portion of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51 can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51.

[0262] A nucleic acid used in the methods of the invention can be amplified using cDNA, mRNA or, alternatively, genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. Furthermore, oligonucleotides corresponding to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleotide sequences can be prepared by standard synthetic techniques, e.g., using an automated DNA synthesizer.

[0263] In a preferred embodiment, the isolated nucleic acid molecules used in the methods of the invention comprise the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, a complement of the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, or a portion of any of these nucleotide sequences. A nucleic acid molecule which is complementary to the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51 such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51 thereby forming a stable duplex.

[0264] In still another preferred embodiment, an isolated nucleic acid molecule used in the methods of the present invention comprises a nucleotide sequence which is at least about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to the entire length of the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, or a portion of any of this nucleotide sequence.

[0265] Moreover, the nucleic acid molecules used in the methods of the invention can comprise only a portion of the nucleic acid sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, for example, a fragment which can be used as a probe or primer or a fragment encoding a portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, *e.g.*, a biologically active portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, of an anti-sense sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, or of a naturally occurring allelic variant or mutant of SEQ ID

NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51. In one embodiment, a nucleic acid molecule used in the methods of the present invention comprises a nucleotide sequence which is greater than 100, 100-200, 200-300, 300-400, 400-500, 500-600, 600-700, 700-800, 800-900, 900-1000, 1000-1100, 1100-1200, 1200-1300, or more nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51.

[0266] As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences that are significantly identical or homologous to each other remain hybridized to each other. Preferably, the conditions are such that sequences at least about 70%, more preferably at least about 80%, even more preferably at least about 85% or 90% identical to each other remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, Ausubel *et al.*, eds., John Wiley & Sons, Inc. (1995), sections 2, 4 and 6. Additional stringent conditions can be found in *Molecular Cloning: A Laboratory Manual*, Sambrook *et al.*, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989), chapters 7, 9 and 11. A preferred, non-limiting example of stringent hybridization conditions includes hybridization in 4X sodium chloride/sodium citrate (SSC), at about 65-70°C (or hybridization in 4X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 1X SSC, at about 65-70°C. A preferred, non-limiting example of highly stringent hybridization conditions includes hybridization in 1X SSC, at about 65-70°C (or hybridization in 1X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 0.3X SSC, at about 65-70°C. A preferred, non-limiting example of reduced stringency hybridization conditions includes hybridization in 4X SSC, at about 50-60°C (or alternatively hybridization in 6X SSC plus 50% formamide at about 40-45°C) followed by one or more washes in 2X SSC, at about 50-60°C. Ranges intermediate to the above-recited values, *e.g.*, at 65-70°C or at 42-50°C are also intended to be encompassed by the present invention. SSPE (1xSSPE is 0.15M NaCl, 10mM NaH<sub>2</sub>PO<sub>4</sub>, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes each after hybridization is complete. The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature ( $T_m$ ) of the

hybrid, where  $T_m$  is determined according to the following equations. For hybrids less than 18 base pairs in length,  $T_m(^{\circ}\text{C}) = 2(\# \text{ of A + T bases}) + 4(\# \text{ of G + C bases})$ . For hybrids between 18 and 49 base pairs in length,  $T_m(^{\circ}\text{C}) = 81.5 + 16.6(\log_{10}[\text{Na}^+]) + 0.41(\% \text{G+C}) - (600/N)$ , where  $N$  is the number of bases in the hybrid, and  $[\text{Na}^+]$  is the concentration of sodium ions in the hybridization buffer ( $[\text{Na}^+]$  for 1xSSC = 0.165 M). It will also be recognized by the skilled practitioner that additional reagents may be added to hybridization and/or wash buffers to decrease non-specific hybridization of nucleic acid molecules to membranes, for example, nitrocellulose or nylon membranes, including but not limited to blocking agents (*e.g.*, BSA or salmon or herring sperm carrier DNA), detergents (*e.g.*, SDS), chelating agents (*e.g.*, EDTA), Ficoll, PVP and the like. When using nylon membranes, in particular, an additional preferred, non-limiting example of stringent hybridization conditions is hybridization in 0.25-0.5M  $\text{NaH}_2\text{PO}_4$ , 7% SDS at about 65°C, followed by one or more washes at 0.02M  $\text{NaH}_2\text{PO}_4$ , 1% SDS at 65°C, see *e.g.*, Church and Gilbert (1984) *Proc. Natl. Acad. Sci. USA* 81:1991-1995, (or alternatively 0.2X SSC, 1% SDS).

[0267] In preferred embodiments, the probe further comprises a label group attached thereto, *e.g.*, the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissue which misexpress a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, such as by measuring a level of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -encoding nucleic acid in a sample of cells from a subject *e.g.*, detecting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA levels or determining whether a genomic 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene has been mutated or deleted.

[0268] The methods of the invention further encompass the use of nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, due to degeneracy of the genetic code and thus encode the same 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735,



1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins as those encoded by the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51. In another embodiment, an isolated nucleic acid molecule included in the methods of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52.

[0269] The methods of the invention further include the use of allelic variants of human 34021, 1720, 1683, 1552, 1682, 1675, 12825, 9952, 5816, 10002 or 1611, *e.g.*, functional and non-functional allelic variants. Functional allelic variants are naturally occurring amino acid sequence variants of the human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein that maintain a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. Functional allelic variants will typically contain only conservative substitution of one or more amino acids of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52 or substitution, deletion or insertion of non-critical residues in non-critical regions of the protein.

[0270] Non-functional allelic variants are naturally occurring amino acid sequence variants of the human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein that do not have a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. Non-functional allelic variants will typically contain a non-conservative substitution, deletion, or insertion or premature truncation of the amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52, or a substitution, insertion or deletion in critical residues or critical regions of the protein.

[0271] The methods of the present invention may further use non-human orthologues of the human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Orthologues of the human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein are proteins that are

isolated from non-human organisms and possess the same 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity.

[0272] The methods of the present invention further include the use of nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51 or a portion thereof, in which a mutation has been introduced. The mutation may lead to amino acid substitutions at "non-essential" amino acid residues or at "essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 (*e.g.*, the sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52) without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins of the present invention are not likely to be amenable to alteration.

[0273] Mutations can be introduced into SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, glycine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein is preferably replaced with another amino

acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, the encoded protein can be expressed recombinantly and the activity of the protein can be determined using the assay described herein.

**[0274]** Another aspect of the invention pertains to the use of isolated nucleic acid molecules which are antisense to the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51. An "antisense" nucleic acid comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 coding strand, or to only a portion thereof. In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (also referred to as 5' and 3' untranslated regions).

**[0275]** Given the coding strand sequences encoding 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735,

1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic

acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest). Antisense nucleic acid molecules used in the methods of the invention are further described above, in section IV.

[0276] In yet another embodiment, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules used in the methods of the present invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acid molecules can be modified to generate peptide nucleic acids (see Hyrup B. *et al.* (1996) *Bioorganic & Medicinal Chemistry* 4 (1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci.* 93:14670-675.

[0277] PNAs of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules can be used in the therapeutic and diagnostic applications described herein. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, for example, inducing transcription or translation arrest or inhibiting replication. PNAs of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules can also be used in the analysis of single base pair mutations in a gene, (*e.g.*, by PNA-directed PCR clamping); as 'artificial restriction enzymes' when used in combination with other enzymes, (*e.g.*, S1 nucleases (Hyrup B. *et al.* (1996) *supra*)); or as probes or primers for DNA sequencing or hybridization (Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* (1996) *supra*).

[0278] In another embodiment, PNAs of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220,

17822, 33945, 43748, 47161, 81982 or 46777 can be modified, (*e.g.*, to enhance their stability or cellular uptake), by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules can be generated which may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, (*e.g.*, RNase H and DNA polymerases), to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup B. *et al.* (1996) *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup B. *et al.* (1996) *supra* and Finn P.J. *et al.* (1996) *Nucleic Acids Res.* 24 (17): 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs, *e.g.*, 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used as a between the PNA and the 5' end of DNA (Mag, M. *et al.* (1989) *Nucleic Acid Res.* 17: 5973-88). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn P.J. *et al.* (1996) *supra*). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser, K.H. *et al.* (1975) *Bioorganic Med. Chem. Lett.* 5: 1119-11124).

[0279] In other embodiments, the oligonucleotide used in the methods of the invention may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. W088/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (See, *e.g.*, Krol *et al.* (1988) *Bio-Techniques* 6:958-976) or intercalating agents. (See, *e.g.*, Zon (1988) *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, or hybridization-triggered cleavage agent).

VII. Isolated 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 Proteins and Anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 Antibodies Used in the Methods of the Invention

[0280] The methods of the invention include the use of isolated 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies. In one embodiment, native 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

[0281] As used herein, a "biologically active portion" of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein includes a fragment of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein having a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. Biologically active portions of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein include peptides comprising amino acid sequences sufficiently identical to or derived from the

amino acid sequence of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, *e.g.*, the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52, which include fewer amino acids than the full length 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins, and exhibit at least one activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein (*e.g.*, the N-terminal region of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein that is believed to be involved in the regulation of apoptotic activity). A biologically active portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be a polypeptide which is, for example, 25, 50, 75, 100, 125, 150, 175, 200, 250, 300 or more amino acids in length. Biologically active portions of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be used as targets for developing agents which modulate a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity.

[0282] In a preferred embodiment, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein used in the methods of the invention has an amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52. In other embodiments, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein is substantially identical to SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26,



28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52, and retains the functional activity of the protein of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail in subsection V above. Accordingly, in another embodiment, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein used in the methods of the invention is a protein which comprises an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52.

[0283] To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, even more preferably at least 60%, and even more preferably at least 70%, 80%, or 90% of the length of the reference sequence (*e.g.*, when aligning a second sequence to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52, having 500 amino acid residues, at least 75, preferably at least 150, more preferably at least 225, even more preferably at least 300, and even more preferably at least 400 or more amino acid residues are aligned). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

[0284] The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred

embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package using either a Blosum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (*Comput. Appl. Biosci.* 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0 or 2.0U), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

[0285] The methods of the invention may also use 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 chimeric or fusion proteins. As used herein, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 "chimeric protein" or "fusion protein" comprises a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide operatively linked to a non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide. An "9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 molecule, whereas a "non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein which is not substantially homologous to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, *e.g.*, a protein which is

different from the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein and which is derived from the same or a different organism. Within a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion protein the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide can correspond to all or a portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. In a preferred embodiment, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion protein comprises at least one biologically active portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. In another preferred embodiment, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion protein comprises at least two biologically active portions of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Within the fusion protein, the term "operatively linked" is intended to indicate that the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide and the non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide are fused in-frame to each other. The non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide can be fused to the N-terminus or C-terminus of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide.

[0286] For example, in one embodiment, the fusion protein is a GST-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644,

19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion protein in which the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences are fused to the C-terminus of the GST sequences. Such fusion proteins can facilitate the purification of recombinant 34021, 1720, 1683, 1552, 1682, 1675, 12825, 9952, 5816, 10002 or 1611.

[0287] In another embodiment, this fusion protein is a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be increased through use of a heterologous signal sequence.

[0288] The 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion proteins used in the methods of the invention can be incorporated into pharmaceutical compositions and administered to a subject *in vivo*. The 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion proteins can be used to affect the bioavailability of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate. Use of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion proteins may be useful therapeutically for the treatment of disorders caused by, for example, (i) aberrant modification or mutation of a gene encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein; (ii) mis-regulation of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene; and (iii) aberrant post-translational modification of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397,

13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

[0289] Moreover, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -fusion proteins used in the methods of the invention can be used as immunogens to produce anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies in a subject, to purify 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 ligands and in screening assays to identify molecules which inhibit the interaction of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate.

[0290] Preferably, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 chimeric or fusion protein used in the methods of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). A 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -encoding

nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

[0291] The present invention also pertains to the use of variants of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins which function as either 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 agonists (mimetics) or as 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antagonists. Variants of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. An agonist of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. An antagonist of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can inhibit one or more of the activities of the naturally occurring form of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein by, for example, competitively modulating a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777-mediated activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Thus, specific biological effects can be elicited by treatment with a variant of limited

function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

[0292] In one embodiment, variants of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein which function as either 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 agonists (mimetics) or as 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein for 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein agonist or antagonist activity. In one embodiment, a variegated library of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences therein. There are a variety of methods which can be used to produce libraries of potential 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397,

13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 variants from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, e.g., Narang, S.A. (1983) *Tetrahedron* 39:3; Itakura *et al.* (1984) *Annu. Rev. Biochem.* 53:323; Itakura *et al.* (1984) *Science* 198:1056; Ike *et al.* (1983) *Nucleic Acid Res.* 11:477).

[0293] In addition, libraries of fragments of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein coding sequence can be used to generate a variegated population of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fragments for screening and subsequent selection of variants of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal, C-terminal and internal fragments of various sizes of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

[0294] Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA



libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 variants (Arkin and Yourvan (1992) *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.* (1993) *Protein Engineering* 6(3):327-331).

[0295] The methods of the present invention further include the use of anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies. An isolated 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, or a portion or fragment thereof, can be used as an immunogen to generate antibodies that bind 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 using standard techniques for polyclonal and monoclonal antibody preparation. A full-length 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be used or, alternatively, antigenic peptide fragments of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be used as immunogens. The antigenic peptide of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 comprises at least 8 amino acid residues of the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48,

50 or 52, and encompasses an epitope of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 such that an antibody raised against the peptide forms a specific immune complex with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Preferably, the antigenic peptide comprises at least 10 amino acid residues, more preferably at least 15 amino acid residues, even more preferably at least 20 amino acid residues, and most preferably at least 30 amino acid residues.

[0296] Preferred epitopes encompassed by the antigenic peptide are regions of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 that are located on the surface of the protein, *e.g.*, hydrophilic regions, as well as regions with high antigenicity.

[0297] A 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 immunogen is typically used to prepare antibodies by immunizing a suitable subject, (*e.g.*, rabbit, goat, mouse, or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or a chemically synthesized 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent. Immunization of a suitable subject with an immunogenic 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 preparation induces a polyclonal anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody response.

[0298] The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which specifically binds (immunoreacts with) an antigen,

such as a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')<sub>2</sub> fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 molecules. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777. A monoclonal antibody composition thus typically displays a single binding affinity for a particular 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein with which it immunoreacts.

[0299] Polyclonal anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies can be prepared as described above by immunizing a suitable subject with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 immunogen. The anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777. If desired, the antibody molecules directed against 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be isolated from the mammal (*e.g.*, from the blood) and further purified by well known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, *e.g.*, when the anti-

9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497) (see also, Brown *et al.* (1981) *J. Immunol.* 127:539-46; Brown *et al.* (1980) *J. Biol. Chem.* 255:4980-83; Yeh *et al.* (1976) *Proc. Natl. Acad. Sci. USA* 76:2927-31; and Yeh *et al.* (1982) *Int. J. Cancer* 29:269-75), the more recent human B cell hybridoma technique (Kozbor *et al.* (1983) *Immunol Today* 4:72), the EBV-hybridoma technique (Cole *et al.* (1985) *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing monoclonal antibody hybridomas is well known (see generally Kenneth, R. H. in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); Lerner, E. A. (1981) *Yale J. Biol. Med.* 54:387-402; Gefter, M. L. *et al.* (1977) *Somatic Cell Genet.* 3:231-36). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777.

[0300] Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 monoclonal antibody (see, *e.g.*, G. Galfre *et al.* (1977) *Nature* 266:55052; Gefter *et al.* (1977) *supra*; Lerner (1981) *supra*; and Kenneth (1980) *supra*). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (*e.g.*, a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium

containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, *e.g.*, the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC. Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777, *e.g.*, using a standard ELISA assay.

[0301] Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 to thereby isolate immunoglobulin library members that bind 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* PCT International Publication No. WO 92/18619; Dower *et al.* PCT International Publication No. WO 91/17271; Winter *et al.* PCT International Publication WO 92/20791; Markland *et al.* PCT International Publication No. WO 92/15679; Breitling *et al.* PCT International Publication WO 93/01288; McCafferty *et al.* PCT International Publication No. WO 92/01047; Garrard *et al.* PCT International Publication No. WO 92/09690; Ladner *et al.* PCT International Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse

*et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J. Mol. Biol.* 226:889-896; Clarkson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:3576-3580; Garrad *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc. Acid Res.* 19:4133-4137; Barbas *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:7978-7982; and McCafferty *et al.* (1990) *Nature* 348:552-554.

[0302] Additionally, recombinant anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the methods of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in Robinson *et al.* International Application No. PCT/US86/02269; Akira, *et al.* European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison *et al.* European Patent Application 173,494; Neuberger *et al.* PCT International Publication No. WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.* European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Canc. Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison, S. L. (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *BioTechniques* 4:214; Winter U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

[0303] An anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody can be used to detect 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865,

12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{35}\text{S}$  or  $^3\text{H}$ .

[0304] This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figure and the Sequence Listing is incorporated herein by reference.

## EXAMPLES

### EXAMPLE 1: TISSUE DISTRIBUTION OF USING TAQMAN™ ANALYSIS

[0305] This example describes the TaqMan™ procedure. The Taqman™ procedure is a quantitative, reverse transcription PCR-based approach for detecting mRNA. The RT-PCR reaction exploits the 5' nuclease activity of AmpliTaq Gold™ DNA Polymerase to cleave a TaqMan™ probe during PCR. Briefly, cDNA was generated from the samples of interest, *e.g.*, heart, kidney, liver, skeletal muscle, and various vessels, and used as the starting material for PCR amplification. In addition to the 5' and 3' gene-specific primers, a gene-specific oligonucleotide probe (complementary to the region being amplified) was included in the reaction (*i.e.*, the Taqman™ probe). The TaqMan™ probe includes the oligonucleotide with a fluorescent reporter dye covalently linked to the 5' end

of the probe (such as FAM (6-carboxyfluorescein), TET (6-carboxy-4,7,2',7'-tetrachlorofluorescein), JOE (6-carboxy-4,5-dichloro-2,7-dimethoxyfluorescein), or VIC) and a quencher dye (TAMRA (6-carboxy-N,N,N',N'-tetramethylrhodamine) at the 3' end of the probe.

[0306] During the PCR reaction, cleavage of the probe separates the reporter dye and the quencher dye, resulting in increased fluorescence of the reporter. Accumulation of PCR products is detected directly by monitoring the increase in fluorescence of the reporter dye. When the probe is intact, the proximity of the reporter dye to the quencher dye results in suppression of the reporter fluorescence. During PCR, if the target of interest is present, the probe specifically anneals between the forward and reverse primer sites. The 5'-3' nucleolytic activity of the AmpliTaq™ Gold DNA Polymerase cleaves the probe between the reporter and the quencher only if the probe hybridizes to the target. The probe fragments are then displaced from the target, and polymerization of the strand continues. The 3' end of the probe is blocked to prevent extension of the probe during PCR. This process occurs in every cycle and does not interfere with the exponential accumulation of product. RNA was prepared using the trizol method and treated with DNase to remove contaminating genomic DNA. cDNA was synthesized using standard techniques. Mock cDNA synthesis in the absence of reverse transcriptase resulted in samples with no detectable PCR amplification of the control gene confirms efficient removal of genomic DNA contamination.

### **Equivalents**

[0307] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.



What is claimed:

1. A method for identifying a compound capable of treating AIDS or an HIV-related disorder, comprising:
  - a) combining a compound to be tested with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide under conditions suitable for binding of the test compound to the polypeptide; and
  - b) detecting binding of the test compound to the polypeptide to thereby identify a compound which binds to the polypeptide, thereby identifying a compound capable of treating AIDS or an HIV-related disorder.
2. The method of claim 1, wherein the compound is selected from the group consisting of a small molecule, a peptide or an antibody.
3. The method of claim 1, wherein the polypeptide further comprises heterologous sequences.
4. The method of claim 1, wherein the polypeptide is an isolated polypeptide, a membrane-bound form of an isolated polypeptide or a cell comprising the polypeptide.
5. The method of claim 4, wherein the cell is an AIDS- or HIV-related cell.
6. The method of claim 1, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:
  - a) a competition binding assay;
  - b) an immunoassay; and
  - c) a yeast two-hybrid assay.
7. A method for identifying a compound capable of treating AIDS or an HIV-related disorder, comprising:
  - a) combining a compound to be tested with a host cell expressing a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777

polypeptide under conditions suitable for binding of the test compound to the polypeptide;  
and

b) detecting binding of the test compound to the polypeptide to thereby identify a compound which binds to the polypeptide, thereby identifying a compound capable of treating AIDS or an HIV-related disorder.

8. The method of claim 7, wherein the compound is selected from the group consisting of a small molecule, a peptide, an antibody or an antisense nucleic acid molecule.

9. The method of claim 7, wherein the polypeptide further comprises heterologous sequences.

10. The method of claim 7, wherein the host cell is an AIDS- or HIV-related cell.

11. The method of claim 7, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:

- a) a competition binding assay;
- b) an immunoassay; and
- c) a yeast two-hybrid assay.

12. A method of identifying a subject having AIDS or an HIV-related disorder, or at risk for developing AIDS or an HIV-related disorder comprising:

a) contacting a sample obtained from the subject comprising polypeptides with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding substance; and

b) detecting the presence of a polypeptide in the sample that binds to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding substance, thereby identifying a subject having AIDS or an HIV-related disorder, or at risk for developing AIDS or an HIV-related disorder.

13. The method of claim 12, wherein the binding substance is an antibody.
14. The method of claim 12, wherein the binding substance is detectably labeled.
15. A method for treating a subject having AIDS or an HIV-related disorder characterized by aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide activity or aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid expression comprising administering to the subject a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator, thereby treating said subject having AIDS or an HIV-related disorder.
16. The method of claim 15, wherein the disorder is a disorder associated with but not limited to AIDS or an HIV-related disorder.
17. The method of claim 15, wherein the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator is administered in a pharmaceutically acceptable formulation.
18. The method of claim 15, wherein the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator is capable of modulating 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide activity.
19. The method of claim 18, wherein the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator is an anti-9145, 1725,

311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody.

20. The method of claim 15, wherein the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator is capable of modulating 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid expression.

## SEQUENCE LISTING

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AIDS AND HIV-RELATED DISORDERS USING 9145, 1725, 311, 837,  
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300	305	310	
acc tgg tcc aac atc tat gac ttg gtg gtg ccc ttc cct tca gcc ccc			1012
Thr Trp Ser Asn Ile Tyr Asp Leu Val Val Pro Phe Pro Ser Ala Pro			
315	320	325	
tcg atg gac acc aca gag gct atg cta aag cag ggc tgg acg ccc agg			1060
Ser Met Asp Thr Thr Glu Ala Met Leu Lys Gln Gly Trp Thr Pro Arg			
330	335	340	
agg atg ttt aag gag gct gat gat ttc ttc acc tcc ctg ggg ctg ctg			1108
Arg Met Phe Lys Glu Ala Asp Asp Phe Phe Thr Ser Leu Gly Leu Leu			
345	350	355	360
ccc gtg cct cct gag ttc tgg aac aag tcg atg ctg gag aag cca acc			1156
Pro Val Pro Pro Glu Phe Trp Asn Lys Ser Met Leu Glu Lys Pro Thr			
365	370	375	
gac ggg cgg gag gtg gtc tgc cac gcc tcg gcc tgg gac ttc tac aac			1204
Asp Gly Arg Glu Val Val Cys His Ala Ser Ala Trp Asp Phe Tyr Asn			
380	385	390	
ggc aag gac ttc cgg atc aag cag tgc acc acc gtg aac ttg gag gac			1252
Gly Lys Asp Phe Arg Ile Lys Gln Cys Thr Thr Val Asn Leu Glu Asp			
395	400	405	
ctg gtg gtg gcc cac cac gaa atg ggc cac atc cag tat ttc atg cag			1300
Leu Val Val Ala His His Glu Met Gly His Ile Gln Tyr Phe Met Gln			
410	415	420	
tac aaa gac tta cct gtg gcc ttg agg gag ggt gcc aac ccc ggc ttc			1348
Tyr Lys Asp Leu Pro Val Ala Leu Arg Glu Gly Ala Asn Pro Gly Phe			
425	430	435	440
cat gag gcc att ggg gac gtg cta gcc ctc tca gtg tct acg ccc aag			1396
His Glu Ala Ile Gly Asp Val Leu Ala Leu Ser Val Ser Thr Pro Lys			
445	450	455	

cac ctg cac agt ctc aac ctg ctg agc agt gag ggt ggc agc gac gag His Leu His Ser Leu Asn Leu Leu Ser Ser Glu Gly Gly Ser Asp Glu 460 465 470	1444
cat gac atc aac ttt ctg atg aag atg gcc ctt gac aag atc gcc ttt His Asp Ile Asn Phe Leu Met Lys Met Ala Leu Asp Lys Ile Ala Phe 475 480 485	1492
atc ccc ttc agc tac ctc gtc gat cag tgg cgc tgg agg gta ttt gat Ile Pro Phe Ser Tyr Leu Val Asp Gln Trp Arg Trp Arg Val Phe Asp 490 495 500	1540
gga agc atc acc aag gag aac tat aac cag gag tgg tgg agc ctc agg Gly Ser Ile Thr Lys Glu Asn Tyr Asn Gln Glu Trp Trp Ser Leu Arg 505 510 515 520	1588
ctg aag tac cag ggc ctc tgc ccc cca gtg ccc agg act caa ggt gac Leu Lys Tyr Gln Gly Leu Cys Pro Pro Val Pro Arg Thr Gln Gly Asp 525 530 535	1636
ttt gac cca ggg gcc aag ttc cac att cct tct agc gtg cct tac atc Phe Asp Pro Gly Ala Lys Phe His Ile Pro Ser Ser Val Pro Tyr Ile 540 545 550	1684
agg tac ttt gtc agc ttc atc atc cag ttc cag ttc cac gag gca ctg Arg Tyr Phe Val Ser Phe Ile Ile Gln Phe Gln Phe His Glu Ala Leu 555 560 565	1732
tgc cag gca gct ggc cac acg ggc ccc ctg cac aag tgt gac atc tac Cys Gln Ala Ala Gly His Thr Gly Pro Leu His Lys Cys Asp Ile Tyr 570 575 580	1780
cag tcc aag gag gcc ggg cag cgc ctg gcg acc gcc atg aag ctg ggc Gln Ser Lys Glu Ala Gly Gln Arg Leu Ala Thr Ala Met Lys Leu Gly 585 590 595 600	1828
ttc agt agg ccg tgg ccg gaa gcc atg cag ctg atc acg ggc cag ccc Phe Ser Arg Pro Trp Pro Glu Ala Met Gln Leu Ile Thr Gly Gln Pro 605 610 615	1876
aac atg agc gcc tcg gcc atg ttg agc tac ttc aag ccg ctg ctg gac Asn Met Ser Ala Ser Ala Met Leu Ser Tyr Phe Lys Pro Leu Leu Asp 620 625 630	1924
tgg ctc cgc acg gag aac gag ctg cat ggg gag aag ctg ggc tgg ccg Trp Leu Arg Thr Glu Asn Glu Leu His Gly Glu Lys Leu Gly Trp Pro 635 640 645	1972
cag tac aac tgg acg ccg aac tcc gct cgc tca gaa ggg ccc ctc cca Gln Tyr Asn Trp Thr Pro Asn Ser Ala Arg Ser Glu Gly Pro Leu Pro 650 655 660	2020
gac agc ggc cgc gtc agc ttc ctg ggc ctg gac ctg gat gcg cag cag Asp Ser Gly Arg Val Ser Phe Leu Gly Leu Asp Leu Asp Ala Gln Gln 665 670 675 680	2068
gcc cgc gtg ggc cag tgg ctg ctg ctc ttc ctg ggc atc gcc ctg ctg Ala Arg Val Gly Gln Trp Leu Leu Leu Phe Leu Gly Ile Ala Leu Leu 685 690 695	2116

gta gcc acc ctg ggc ctc agc cag cgg ctc ttc agc atc cgc cac cgc 2164  
 Val Ala Thr Leu Gly Leu Ser Gln Arg Leu Phe Ser Ile Arg His Arg  
 700 705 710

agc ctc cac cgg cac tcc cac ggg ccc cag ttc ggc tcc gag gtg gag 2212  
 Ser Leu His Arg His Ser His Gly Pro Gln Phe Gly Ser Glu Val Glu  
 715 720 725

ctg aga cac tcc tga ggtgacccgg ctgggtcggc cctgcccagg ggcctccac 2267  
 Leu Arg His Ser \*  
 730

cagagactgg gatgggaaca ctgggtgggca gctgaggaca caccacacac cccagccac 2327  
 cctgtcctc ctgccctgtc cctgtccccc tcccctacca gtccctccacc accagccgcc 2387  
 ccagccctt ctcccagcac acggctgcct gacactgagc cccacctctc caagtctccc 2447  
 tgtgaatata attaaaggct ctgccctccc a 2478

<210> 4

<211> 732

<212> PRT

<213> Homo sapiens

<400> 4

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 Leu Leu Cys Tyr Gly His Pro Leu Leu Val Pro Ser Gln Glu Ala Ser  
 20 25 30  
 Gln Gln Val Thr Val Thr His Gly Thr Ser Ser Gln Ala Thr Thr Ser  
 35 40 45  
 Ser Gln Thr Thr Thr His Gln Ala Thr Ala His Gln Thr Ser Ala Gln  
 50 55 60  
 Ser Pro Asn Leu Val Thr Asp Glu Ala Glu Ala Ser Lys Phe Val Glu  
 65 70 75 80  
 Glu Tyr Asp Arg Thr Ser Gln Val Val Trp Asn Glu Tyr Ala Glu Ala  
 85 90 95  
 Asn Trp Asn Tyr Asn Thr Asn Ile Thr Thr Glu Thr Ser Lys Ile Leu  
 100 105 110  
 Leu Gln Lys Asn Met Gln Ile Ala Asn His Thr Leu Lys Tyr Gly Thr  
 115 120 125  
 Gln Ala Arg Lys Phe Asp Val Asn Gln Leu Gln Asn Thr Thr Ile Lys  
 130 135 140  
 Arg Ile Ile Lys Lys Val Gln Asp Leu Glu Arg Ala Ala Leu Pro Ala  
 145 150 155 160  
 Gln Glu Leu Glu Glu Tyr Asn Lys Ile Leu Leu Asp Met Glu Thr Thr  
 165 170 175  
 Tyr Ser Val Ala Thr Val Cys His Pro Asn Gly Ser Cys Leu Gln Leu  
 180 185 190  
 Glu Pro Asp Leu Thr Asn Val Met Ala Thr Ser Arg Lys Tyr Glu Asp  
 195 200 205  
 Leu Leu Trp Ala Trp Glu Gly Trp Arg Asp Lys Ala Gly Arg Ala Ile  
 210 215 220  
 Leu Gln Phe Tyr Pro Lys Tyr Val Glu Leu Ile Asn Gln Ala Ala Arg  
 225 230 235 240  
 Leu Asn Gly Tyr Val Asp Ala Gly Asp Ser Trp Arg Ser Met Tyr Glu  
 245 250 255  
 Thr Pro Ser Leu Glu Gln Asp Leu Glu Arg Leu Phe Gln Glu Leu Gln  
 260 265 270  
 Pro Leu Tyr Leu Asn Leu His Ala Tyr Val Arg Arg Ala Leu His Arg  
 275 280 285  
 His Tyr Gly Ala Gln His Ile Asn Leu Glu Gly Pro Ile Pro Ala His  
 290 295 300

Leu Leu Gly Asn Met Trp Ala Gln Thr Trp Ser Asn Ile Tyr Asp Leu  
 305 310 315 320  
 Val Val Pro Phe Pro Ser Ala Pro Ser Met Asp Thr Thr Glu Ala Met  
 325 330 335  
 Leu Lys Gln Gly Trp Thr Pro Arg Arg Met Phe Lys Glu Ala Asp Asp  
 340 345 350  
 Phe Phe Thr Ser Leu Gly Leu Leu Pro Val Pro Pro Glu Phe Trp Asn  
 355 360 365  
 Lys Ser Met Leu Glu Lys Pro Thr Asp Gly Arg Glu Val Val Cys His  
 370 375 380  
 Ala Ser Ala Trp Asp Phe Tyr Asn Gly Lys Asp Phe Arg Ile Lys Gln  
 385 390 395 400  
 Cys Thr Thr Val Asn Leu Glu Asp Leu Val Val Ala His His Glu Met  
 405 410 415  
 Gly His Ile Gln Tyr Phe Met Gln Tyr Lys Asp Leu Pro Val Ala Leu  
 420 425 430  
 Arg Glu Gly Ala Asn Pro Gly Phe His Glu Ala Ile Gly Asp Val Leu  
 435 440 445  
 Ala Leu Ser Val Ser Thr Pro Lys His Leu His Ser Leu Asn Leu Leu  
 450 455 460  
 Ser Ser Glu Gly Gly Ser Asp Glu His Asp Ile Asn Phe Leu Met Lys  
 465 470 475 480  
 Met Ala Leu Asp Lys Ile Ala Phe Ile Pro Phe Ser Tyr Leu Val Asp  
 485 490 495  
 Gln Trp Arg Trp Arg Val Phe Asp Gly Ser Ile Thr Lys Glu Asn Tyr  
 500 505 510  
 Asn Gln Glu Trp Trp Ser Leu Arg Leu Lys Tyr Gln Gly Leu Cys Pro  
 515 520 525  
 Pro Val Pro Arg Thr Gln Gly Asp Phe Asp Pro Gly Ala Lys Phe His  
 530 535 540  
 Ile Pro Ser Ser Val Pro Tyr Ile Arg Tyr Phe Val Ser Phe Ile Ile  
 545 550 555 560  
 Gln Phe Gln Phe His Glu Ala Leu Cys Gln Ala Ala Gly His Thr Gly  
 565 570 575  
 Pro Leu His Lys Cys Asp Ile Tyr Gln Ser Lys Glu Ala Gly Gln Arg  
 580 585 590  
 Leu Ala Thr Ala Met Lys Leu Gly Phe Ser Arg Pro Trp Pro Glu Ala  
 595 600 605  
 Met Gln Leu Ile Thr Gly Gln Pro Asn Met Ser Ala Ser Ala Met Leu  
 610 615 620  
 Ser Tyr Phe Lys Pro Leu Leu Asp Trp Leu Arg Thr Glu Asn Glu Leu  
 625 630 635 640  
 His Gly Glu Lys Leu Gly Trp Pro Gln Tyr Asn Trp Thr Pro Asn Ser  
 645 650 655  
 Ala Arg Ser Glu Gly Pro Leu Pro Asp Ser Gly Arg Val Ser Phe Leu  
 660 665 670  
 Gly Leu Asp Leu Asp Ala Gln Gln Ala Arg Val Gly Gln Trp Leu Leu  
 675 680 685  
 Leu Phe Leu Gly Ile Ala Leu Leu Val Ala Thr Leu Gly Leu Ser Gln  
 690 695 700  
 Arg Leu Phe Ser Ile Arg His Arg Ser Leu His Arg His Ser His Gly  
 705 710 715 720  
 Pro Gln Phe Gly Ser Glu Val Glu Leu Arg His Ser  
 725 730

&lt;210&gt; 5

&lt;211&gt; 2051

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (61)...(1224)

&lt;400&gt; 5

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atg aat cgg cac cat ctg cag gat cac ttt ctg gaa ata gac aag aag 108
Met Asn Arg His His Leu Gln Asp His Phe Leu Glu Ile Asp Lys Lys
  1             5             10             15

aac tgc tgt gtg ttc cga gat gac ttc att gcc aag gtg ttg ccg ccg 156
Asn Cys Cys Val Phe Arg Asp Asp Phe Ile Ala Lys Val Leu Pro Pro
      20             25             30

gtg ttg ggg ctg gag ttt atc ttt ggg ctt ctg ggc aat ggc ctt gcc 204
Val Leu Gly Leu Glu Phe Ile Phe Gly Leu Leu Gly Asn Gly Leu Ala
      35             40             45

ctg tgg att ttc tgt ttc cac ctc aag tcc tgg aaa tcc agc cgg att 252
Leu Trp Ile Phe Cys Phe His Leu Lys Ser Trp Lys Ser Ser Arg Ile
      50             55             60

ttc ctg ttc aac ctg gca gta gct gac ttt cta ctg atc atc tgc ctg 300
Phe Leu Phe Asn Leu Ala Val Ala Asp Phe Leu Leu Ile Ile Cys Leu
      65             70             75

ccg ttc gtg atg gac tac tat gtg cgg cgt tca gac tgg aac ttt ggg 348
Pro Phe Val Met Asp Tyr Tyr Val Arg Arg Ser Asp Trp Asn Phe Gly
      85             90             95

gac atc cct tgc cgg ctg gtg ctc ttc atg ttt gcc atg aac cgc cag 396
Asp Ile Pro Cys Arg Leu Val Leu Phe Met Phe Ala Met Asn Arg Gln
      100            105            110

ggc agc atc atc ttc ctc acg gtg gtg gcg gta gac agg tat ttc cgg 444
Gly Ser Ile Ile Phe Leu Thr Val Val Ala Val Asp Arg Tyr Phe Arg
      115            120            125

gtg gtc cat ccc cac cac gcc ctg aac aag atc tcc aat tgg aca gca 492
Val Val His Pro His His Ala Leu Asn Lys Ile Ser Asn Trp Thr Ala
      130            135            140

gcc atc atc tct tgc ctt ctg tgg ggc atc act gtt ggc cta aca gtc 540
Ala Ile Ile Ser Cys Leu Leu Trp Gly Ile Thr Val Gly Leu Thr Val
      145            150            155            160

cac ctc ctg aag aag aag ttg ctg atc cag aat ggc cct gca aat gtg 588
His Leu Leu Lys Lys Lys Leu Leu Ile Gln Asn Gly Pro Ala Asn Val
      165            170            175

tgc atc agc ttc agc atc tgc cat acc ttc cgg tgg cac gaa gct atg 636
Cys Ile Ser Phe Ser Ile Cys His Thr Phe Arg Trp His Glu Ala Met
      180            185            190

ttc ctc ctg gag ttc ctc ctg ccc ctg ggc atc atc ctg ttc tgc tca 684
Phe Leu Leu Glu Phe Leu Leu Pro Leu Gly Ile Ile Leu Phe Cys Ser
      195            200            205

gcc aga att atc tgg agc ctg cgg cag aga caa atg gac cgg cat gcc 732
Ala Arg Ile Ile Trp Ser Leu Arg Gln Arg Gln Met Asp Arg His Ala
      210            215            220

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aag atc aag aga gcc atc acc ttc atc atg gtg gtg gcc atc gtc ttt 780
Lys Ile Lys Arg Ala Ile Thr Phe Ile Met Val Val Ala Ile Val Phe
225                230                235                240

gtc atc tgc ttc ctt ccc agc gtg gtt gtg cgg atc cgc atc ttc tgg 828
Val Ile Cys Phe Leu Pro Ser Val Val Val Arg Ile Arg Ile Phe Trp
                245                250                255

ctc ctg cac act tcg ggc acg cag aat tgt gaa gtg tac cgc tcg gtg 876
Leu Leu His Thr Ser Gly Thr Gln Asn Cys Glu Val Tyr Arg Ser Val
                260                265                270

gac ctg gcg ttc ttt atc act ctc agc ttc acc tac atg aac agc atg 924
Asp Leu Ala Phe Phe Ile Thr Leu Ser Phe Thr Tyr Met Asn Ser Met
                275                280                285

ctg gac ccc gtg gtg tac tac ttc tcc agc cca tcc ttt ccc aac ttc 972
Leu Asp Pro Val Val Tyr Tyr Phe Ser Ser Pro Ser Phe Pro Asn Phe
290                295                300

ttc tcc act ttg atc aac cgc tgc ctc cag agg aag atg aca ggt gag 1020
Phe Ser Thr Leu Ile Asn Arg Cys Leu Gln Arg Lys Met Thr Gly Glu
305                310                315                320

cca gat aat aac cgc agc acg agc gtc gag ctc aca ggg gac ccc aac 1068
Pro Asp Asn Asn Arg Ser Thr Ser Val Glu Leu Thr Gly Asp Pro Asn
                325                330                335

aaa acc aga ggc gct cca gag gcg tta atg gcc aac tcc ggt gag cca 1116
Lys Thr Arg Gly Ala Pro Glu Ala Leu Met Ala Asn Ser Gly Glu Pro
                340                345                350

tgg agc ccc tct tat ctg ggc cca acc tca aat aac cat tcc aag aag 1164
Trp Ser Pro Ser Tyr Leu Gly Pro Thr Ser Asn Asn His Ser Lys Lys
                355                360                365

gga cat tgt cac caa gaa cca gca tct ctg gag aaa cag ttg ggc tgt 1212
Gly His Cys His Gln Glu Pro Ala Ser Leu Glu Lys Gln Leu Gly Cys
                370                375                380

tgc atc gag taa tgtcactgga ctgggcctaa gggttctctgg aacttccaga 1264
Cys Ile Glu *
385

ttcagagaat ctgatttagg gaaactgtgg cagatgagtg ggagactggt tgcaagggtgt 1324
gaccacagga atcctggagg aacagagagt aaagcttcta ggcatctgaa acttgcttca 1384
tctctgacgc tcgcaggact gaagatgggc aaattgtagg cgtttctgct gagcagagtt 1444
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gagcagttaa aacggcttca ggatagaaag ctgtttccca cctgtttcgt tttaccatta 1924
aaagggaaac gtgcctctgc cccacgggta gaggggggtgc acgttctctc tggttccttc 1984
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aaaaaaaaa
2051

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<210> 6  
 <211> 387  
 <212> PRT  
 <213> Homo sapiens

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 Val Leu Gly Leu Glu Phe Ile Phe Gly Leu Leu Gly Asn Gly Leu Ala  
 35 40 45  
 Leu Trp Ile Phe Cys Phe His Leu Lys Ser Trp Lys Ser Ser Arg Ile  
 50 55 60  
 Phe Leu Phe Asn Leu Ala Val Ala Asp Phe Leu Leu Ile Ile Cys Leu  
 65 70 75 80  
 Pro Phe Val Met Asp Tyr Tyr Val Arg Arg Ser Asp Trp Asn Phe Gly  
 85 90 95  
 Asp Ile Pro Cys Arg Leu Val Leu Phe Met Phe Ala Met Asn Arg Gln  
 100 105 110  
 Gly Ser Ile Ile Phe Leu Thr Val Val Ala Val Asp Arg Tyr Phe Arg  
 115 120 125  
 Val Val His Pro His His Ala Leu Asn Lys Ile Ser Asn Trp Thr Ala  
 130 135 140  
 Ala Ile Ile Ser Cys Leu Leu Trp Gly Ile Thr Val Gly Leu Thr Val  
 145 150 155 160  
 His Leu Leu Lys Lys Lys Leu Leu Ile Gln Asn Gly Pro Ala Asn Val  
 165 170 175  
 Cys Ile Ser Phe Ser Ile Cys His Thr Phe Arg Trp His Glu Ala Met  
 180 185 190  
 Phe Leu Leu Glu Phe Leu Leu Pro Leu Gly Ile Ile Leu Phe Cys Ser  
 195 200 205  
 Ala Arg Ile Ile Trp Ser Leu Arg Gln Arg Gln Met Asp Arg His Ala  
 210 215 220  
 Lys Ile Lys Arg Ala Ile Thr Phe Ile Met Val Val Ala Ile Val Phe  
 225 230 235 240  
 Val Ile Cys Phe Leu Pro Ser Val Val Val Arg Ile Arg Ile Phe Trp  
 245 250 255  
 Leu Leu His Thr Ser Gly Thr Gln Asn Cys Glu Val Tyr Arg Ser Val  
 260 265 270  
 Asp Leu Ala Phe Phe Ile Thr Leu Ser Phe Thr Tyr Met Asn Ser Met  
 275 280 285  
 Leu Asp Pro Val Val Tyr Tyr Phe Ser Ser Pro Ser Phe Pro Asn Phe  
 290 295 300  
 Phe Ser Thr Leu Ile Asn Arg Cys Leu Gln Arg Lys Met Thr Gly Glu  
 305 310 315 320  
 Pro Asp Asn Asn Arg Ser Thr Ser Val Glu Leu Thr Gly Asp Pro Asn  
 325 330 335  
 Lys Thr Arg Gly Ala Pro Glu Ala Leu Met Ala Asn Ser Gly Glu Pro  
 340 345 350  
 Trp Ser Pro Ser Tyr Leu Gly Pro Thr Ser Asn Asn His Ser Lys Lys  
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 Gly His Cys His Gln Glu Pro Ala Ser Leu Glu Lys Gln Leu Gly Cys  
 370 375 380  
 Cys Ile Glu  
 385

<210> 7

<211> 2087

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<212> DNA
<213> Homo sapiens

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<221> CDS
<222> (104)...(1612)

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gagacgtgga gcgcgccggc tcgctgcagc tccgggactc aac atg cgc tgc tcg 115
                                         Met Arg Cys Ser
                                         1

cgc gga ggc gtc tgg ctg ggc ctg gcc gcg tcg ctc ctg cac gtg tcc 163
Pro Gly Gly Val Trp Leu Gly Leu Ala Ala Ser Leu Leu His Val Ser
5          10          15          20

ctg caa ggc gag ttc cag agg aag ctt tac aag gag ctg gtc aag aac 211
Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu Leu Val Lys Asn
          25          30          35

tac aat ccc ttg gag agg ccc gtg gcc aat gac tcg caa cca ctc acc 259
Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser Gln Pro Leu Thr
          40          45          50

gtc tac ttc tcc ctg agc ctc ctg cag atc atg gac gtg gat gag aag 307
Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp Val Asp Glu Lys
          55          60          65

aac caa gtt tta acc acc aac att tgg ctg caa atg tct tgg aca gat 355
Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met Ser Trp Thr Asp
          70          75          80

cac tat tta cag tgg aat gtg tca gaa tat cca ggg gtg aag act gtt 403
His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly Val Lys Thr Val
          85          90          95          100

cgt ttc cca gat ggc cag att tgg aaa cca gac att ctt ctc tat aac 451
Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile Leu Leu Tyr Asn
          105          110          115

agt gct gat gag cgc ttt gac gcc aca ttc cac act aac gtg ttg gtg 499
Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr Asn Val Leu Val
          120          125          130

aat tct tct ggg cat tgc cag tac ctg cct cca ggc ata ttc aag agt 547
Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly Ile Phe Lys Ser
          135          140          145

tcc tgc tac atc gat gta cgc tgg ttt ccc ttt gat gtg cag cac tgc 595
Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp Val Gln His Cys
          150          155          160

aaa ctg aag ttt ggg tcc tgg tct tac gga ggc tgg tcc ttg gat ctg 643
Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp Ser Leu Asp Leu
          165          170          175          180

cag atg cag gag gca gat atc agt ggc tat atc ccc aat gga gaa tgg 691
Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro Asn Gly Glu Trp
          185          190          195

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gac cta gtg gga atc ccc ggc aag agg agt gaa agg ttc tat gag tgc	739
Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg Phe Tyr Glu Cys	
200 205 210	
tgc aaa gag ccc tac ccc gat gtc acc ttc aca gtg acc atg cgc cgc	787
Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val Thr Met Arg Arg	
215 220 225	
agg aca ctc tac tat ggc ctc aac ctg ctg atc ccc tgt gtg ctc atc	835
Arg Thr Leu Tyr Tyr Gly Leu Asn Leu Leu Ile Pro Cys Val Leu Ile	
230 235 240	
tcc gcc ctc gcc ctg ctg gtg ttc ctg ctt cct gca gat tcc ggg gag	883
Ser Ala Leu Ala Leu Leu Val Phe Leu Leu Pro Ala Asp Ser Gly Glu	
245 250 255 260	
aag att tcc ctg ggg ata aca gtc tta ctc tct ctt acc gtc ttc atg	931
Lys Ile Ser Leu Gly Ile Thr Val Leu Leu Ser Leu Thr Val Phe Met	
265 270 275	
ctg ctc gtg gct gag atc atg ccc gca aca tcc gat tgc gta cca ttg	979
Leu Leu Val Ala Glu Ile Met Pro Ala Thr Ser Asp Ser Val Pro Leu	
280 285 290	
ata gcc cag tac ttc gcc agc acc atg atc atc gtg ggc ctc tgc gtg	1027
Ile Ala Gln Tyr Phe Ala Ser Thr Met Ile Ile Val Gly Leu Ser Val	
295 300 305	
gtg gtg aca gtg atc gtg ctg cag tac cac cac cac gac ccc gac ggg	1075
Val Val Thr Val Ile Val Leu Gln Tyr His His His Asp Pro Asp Gly	
310 315 320	
ggc aag atg ccc aag tgg acc aga gtc atc ctt ctg aac tgg tgc gcg	1123
Gly Lys Met Pro Lys Trp Thr Arg Val Ile Leu Leu Asn Trp Cys Ala	
325 330 335 340	
tgg ttc ctg cga atg aag agg ccc ggg gag gac aag gtg cgc ccg gcc	1171
Trp Phe Leu Arg Met Lys Arg Pro Gly Glu Asp Lys Val Arg Pro Ala	
345 350 355	
tgc cag cac aag cag cgg cgc tgc agc ctg gcc agt gtg gag atg agc	1219
Cys Gln His Lys Gln Arg Arg Cys Ser Leu Ala Ser Val Glu Met Ser	
360 365 370	
gcc gtg ggc ccg ccg ccc gcc agc aac ggg aac ctg ctg tac atc gcc	1267
Ala Val Gly Pro Pro Pro Ala Ser Asn Gly Asn Leu Leu Tyr Ile Gly	
375 380 385	
ttc cgc ggc ctg gac ggc gtg cac tgt gtc ccg acc ccc gac tct ggg	1315
Phe Arg Gly Leu Asp Gly Val His Cys Val Pro Thr Pro Asp Ser Gly	
390 395 400	
gta gtg tgt ggc cgc atg gcc tgc tcc ccc acg cac gat gag cac ctc	1363
Val Val Cys Gly Arg Met Ala Cys Ser Pro Thr His Asp Glu His Leu	
405 410 415 420	
ctg cac ggc ggg caa ccc ccc gag ggg gac ccg gac ttg gcc aag atc	1411
Leu His Gly Gly Gln Pro Pro Glu Gly Asp Pro Asp Leu Ala Lys Ile	
425 430 435	
ctg gag gag gtc cgc tac att gcc aac cgc ttc cgc tgc cag gac gaa	1459

Leu Glu Glu Val Arg Tyr Ile Ala Asn Arg Phe Arg Cys Gln Asp Glu  
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 agc gag gcg gtc tgc agc gag tgg aag ttc gcc gcc tgt gtg gtg gac 1507  
 Ser Glu Ala Val Cys Ser Glu Trp Lys Phe Ala Ala Cys Val Val Asp  
 455 460 465  
 cgc ctg tgc ctc atg gcc ttc tcg gtc ttc acc atc atc tgc acc atc 1555  
 Arg Leu Cys Leu Met Ala Phe Ser Val Phe Thr Ile Ile Cys Thr Ile  
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 ggc atc ctg atg tcg gct ccc aac ttc gtg gag gcc gtg tcc aaa gac 1603  
 Gly Ile Leu Met Ser Ala Pro Asn Phe Val Glu Ala Val Ser Lys Asp  
 485 490 495 500  
 ttt gcg taa ccacactggg tctgtacatg tggaaaactc acagatgggc 1652  
 Phe Ala \*

aaggcctttg gcttggcgag atttgggggt gctaataccag gacagcatta cagccacaa 1712  
 ctccagtgtt ccttcttggc tgtcagtcgt gttgcttacg gtttctttgt tacttttaggt 1772  
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 gaaagccctt cggagagctc cccatggctc ctcaccaccg agacagtggg ttttgcattg 1952  
 ctgcatgaag gtctacctga aaattcaaca tttgcttttt gcttgtgtac aaaccagat 2012  
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 acaaaaaaaaa aaaaa 2087

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 <212> PRT  
 <213> Homo sapiens

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 Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser  
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 Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp  
 50 55 60  
 Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met  
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 Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly  
 85 90 95  
 Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile  
 100 105 110  
 Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr  
 115 120 125  
 Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly  
 130 135 140  
 Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp  
 145 150 155 160  
 Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp  
 165 170 175  
 Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro  
 180 185 190  
 Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg  
 195 200 205  
 Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val

210	215	220
Thr Met Arg Arg Arg	Thr Leu Tyr Tyr Gly	Leu Asn Leu Leu Ile Pro
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Cys Val Leu Ile Ser	Ala Leu Ala Leu Leu Val	Phe Leu Leu Pro Ala
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Asp Ser Gly Glu Lys	Ile Ser Leu Gly Ile Thr	Val Leu Leu Ser Leu
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Thr Val Phe Met Leu	Leu Val Ala Glu Ile Met	Pro Ala Thr Ser Asp
275	280	285
Ser Val Pro Leu Ile	Ala Gln Tyr Phe Ala Ser	Thr Met Ile Ile Val
290	295	300
Gly Leu Ser Val Val	Val Thr Val Ile Val Leu	Gln Tyr His His His
305	310	315
Asp Pro Asp Gly Gly	Lys Met Pro Lys Trp Thr	Arg Val Ile Leu Leu
325	330	335
Asn Trp Cys Ala Trp	Phe Leu Arg Met Lys Arg	Pro Gly Glu Asp Lys
340	345	350
Val Arg Pro Ala Cys	Gln His Lys Gln Arg Arg	Cys Ser Leu Ala Ser
355	360	365
Val Glu Met Ser Ala	Val Gly Pro Pro Pro Ala	Ser Asn Gly Asn Leu
370	375	380
Leu Tyr Ile Gly Phe	Arg Gly Leu Asp Gly Val	His Cys Val Pro Thr
385	390	395
Pro Asp Ser Gly Val	Val Cys Gly Arg Met Ala	Cys Ser Pro Thr His
405	410	415
Asp Glu His Leu Leu	His Gly Gly Gln Pro Pro	Glu Gly Asp Pro Asp
420	425	430
Leu Ala Lys Ile Leu	Glu Glu Val Arg Tyr Ile	Ala Asn Arg Phe Arg
435	440	445
Cys Gln Asp Glu Ser	Glu Ala Val Cys Ser Glu	Trp Lys Phe Ala Ala
450	455	460
Cys Val Val Asp Arg	Leu Cys Leu Met Ala Phe	Ser Val Phe Thr Ile
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Val Ser Lys Asp Phe	Ala	
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 agccccgggg cgccgcgcgg agagcaagcg gagatagcga ctttgccgcc ccagccctc 180  
 gcctttctgc atcgcttcc ccgcatactc gggctcttct gtcctttccg ctgtcccccac 240  
 cgccgcc atg gcc acc ttg ctc cgc agc aag ctg tcc aac gtg gcc acg 289  
 Met Ala Thr Leu Leu Arg Ser Lys Leu Ser Asn Val Ala Thr  
 1 5 10  
 tcc gtg tcc aac aag tcc cag gcc aag atg agc ggc atg ttc gcc agg 337  
 Ser Val Ser Asn Lys Ser Gln Ala Lys Met Ser Gly Met Phe Ala Arg  
 15 20 25 30

atg ggt ttt cag gcg gcc acg gat gag gag gcg gtg ggc ttc gcg cat 385  
 Met Gly Phe Gln Ala Ala Thr Asp Glu Glu Ala Val Gly Phe Ala His  
 35 40 45

tgc gac gac ctc gac ttt gag cac cgc cag ggc ctg cag atg gac atc 433  
 Cys Asp Asp Leu Asp Phe Glu His Arg Gln Gly Leu Gln Met Asp Ile  
 50 55 60

ctg aaa gcc gag gga gag ccc tgc ggg gac gag ggc gct gaa gcg ccc 481  
 Leu Lys Ala Glu Gly Glu Pro Cys Gly Asp Glu Gly Ala Glu Ala Pro  
 65 70 75

gtc gag gga gac atc cat tat cag cga ggc agc gga gct cct ctg ccg 529  
 Val Glu Gly Asp Ile His Tyr Gln Arg Gly Ser Gly Ala Pro Leu Pro  
 80 85 90

ccc tcc ggc tcc aag gac cag gtg gga ggt ggt ggc gaa ttc ggg ggc 577  
 Pro Ser Gly Ser Lys Asp Gln Val Gly Gly Gly Gly Glu Phe Gly Gly  
 95 100 105 110

cac gac aag ccc aaa atc acg gcg tgg gag gca ggc tgg aac gtg acc 625  
 His Asp Lys Pro Lys Ile Thr Ala Trp Glu Ala Gly Trp Asn Val Thr  
 115 120 125

aac gcc atc cag ggc atg ttc gtg ctg ggc cta ccc tac gcc atc ctg 673  
 Asn Ala Ile Gln Gly Met Phe Val Leu Gly Leu Pro Tyr Ala Ile Leu  
 130 135 140

cac ggc ggc tac ctg ggg ttg ttt ctc atc atc ttc gcc gcc gtt gtg 721  
 His Gly Gly Tyr Leu Gly Leu Phe Leu Ile Ile Phe Ala Ala Val Val  
 145 150 155

tgc tgc tac acc ggc aag atc ctc atc gcg tgc ctg tac gag gag aat 769  
 Cys Cys Tyr Thr Gly Lys Ile Leu Ile Ala Cys Leu Tyr Glu Glu Asn  
 160 165 170

gaa gac ggc gag gtg gtg cgc gtg cgg gac tcg tac gtg gcc ata gcc 817  
 Glu Asp Gly Glu Val Val Arg Val Arg Asp Ser Tyr Val Ala Ile Ala  
 175 180 185 190

aac gcc tgc tgc gcc ccg cgc ttc cca acg ctg ggc ggc cga gtg gtg 865  
 Asn Ala Cys Cys Ala Pro Arg Phe Pro Thr Leu Gly Gly Arg Val Val  
 195 200 205

aac gta gcg cag atc atc gag ctg gtg atg acg tgc atc ctg tac gtg 913  
 Asn Val Ala Gln Ile Ile Glu Leu Val Met Thr Cys Ile Leu Tyr Val  
 210 215 220

gtg gtg agt ggc aac ctc atg tac aac agc ttc ccg ggg ctg ccc gtg 961  
 Val Val Ser Gly Asn Leu Met Tyr Asn Ser Phe Pro Gly Leu Pro Val  
 225 230 235

tcg cag aag tcc tgg tcc att atc gcc acg gcc gtg ctg ctg cct tgc 1009  
 Ser Gln Lys Ser Trp Ser Ile Ile Ala Thr Ala Val Leu Leu Pro Cys  
 240 245 250

gcc ttc ctt aag aac ctc aag gcc gtg tcc aag ttc agt ctg ctg tgc 1057  
 Ala Phe Leu Lys Asn Leu Lys Ala Val Ser Lys Phe Ser Leu Leu Cys  
 255 260 265 270

act ctg gcc cac ttc gtc atc aat atc ctg gtc ata gcc tac tgt cta 1105

Thr Leu Ala His Phe Val Ile Asn Ile Leu Val Ile Ala Tyr Cys Leu	
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tcg cgg gcg cgc gac tgg gcc tgg gag aag gtc aag ttc tac atc gac	1153
Ser Arg Ala Arg Asp Trp Ala Trp Glu Lys Val Lys Phe Tyr Ile Asp	
290 295 300	
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Val Lys Lys Phe Pro Ile Ser Ile Gly Ile Ile Val Phe Ser Tyr Thr	
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tct cag atc ttc ctg cct tcg ctg gag ggc aat atg cag cag ccc agc	1249
Ser Gln Ile Phe Leu Pro Ser Leu Glu Gly Asn Met Gln Gln Pro Ser	
320 325 330	
gag ttc cac tgc atg atg aac tgg acg cac atc gca gcc tgc gtg ctc	1297
Glu Phe His Cys Met Met Asn Trp Thr His Ile Ala Ala Cys Val Leu	
335 340 345 350	
aag ggc ctc ttc gcg ctc gtc gcc tac ctc acc tgg gcc gac gag acc	1345
Lys Gly Leu Phe Ala Leu Val Ala Tyr Leu Thr Trp Ala Asp Glu Thr	
355 360 365	
aag gag gtc atc acg gat aac ctg ccc ggc tcc atc cgc gcc gtg gtc	1393
Lys Glu Val Ile Thr Asp Asn Leu Pro Gly Ser Ile Arg Ala Val Val	
370 375 380	
aac atc ttt ctg gtg gcc aag gcg ctg ttg tcc tat cct ctg cca ttc	1441
Asn Ile Phe Leu Val Ala Lys Ala Leu Leu Ser Tyr Pro Leu Pro Phe	
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Phe Ala Ala Val Glu Val Leu Glu Lys Ser Leu Phe Gln Glu Gly Ser	
400 405 410	
cgc gcc ttt ttc ccg gcc tgc tac agc ggc gac ggg cgc ctg aag tcc	1537
Arg Ala Phe Phe Pro Ala Cys Tyr Ser Gly Asp Gly Arg Leu Lys Ser	
415 420 425 430	
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Trp Gly Leu Thr Leu Arg Cys Ala Leu Val Val Phe Thr Leu Leu Met	
435 440 445	
gcc att tat gtg ccg cac ttc gcg ctg ctc atg ggc ctc acc ggc agc	1633
Ala Ile Tyr Val Pro His Phe Ala Leu Leu Met Gly Leu Thr Gly Ser	
450 455 460	
ctc acg ggc gcc ggc ctc tgt ttc ttg ctg ccc agc ctc ttt cac ctg	1681
Leu Thr Gly Ala Gly Leu Cys Phe Leu Leu Pro Ser Leu Phe His Leu	
465 470 475	
cgc ctg ctc tgg cgc aag ctg ctg tgg cac caa gtc ttc ttc gac gtc	1729
Arg Leu Leu Trp Arg Lys Leu Leu Trp His Gln Val Phe Phe Asp Val	
480 485 490	
gcc atc ttc gtc atc ggc ggc atc tgc agc gtg tcc ggc ttc gtg cac	1777
Ala Ile Phe Val Ile Gly Gly Ile Cys Ser Val Ser Gly Phe Val His	
495 500 505 510	
tcc ctc gag ggc ctc atc gaa gcc tac cga acc aac gcg gag gac tag	1825
Ser Leu Glu Gly Leu Ile Glu Ala Tyr Arg Thr Asn Ala Glu Asp *	

515

520

525

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&lt;210&gt; 10

&lt;211&gt; 525

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 10

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20          25          30
Phe Gln Ala Ala Thr Asp Glu Glu Ala Val Gly Phe Ala His Cys Asp
35          40          45
Asp Leu Asp Phe Glu His Arg Gln Gly Leu Gln Met Asp Ile Leu Lys
50          55          60
Ala Glu Gly Glu Pro Cys Gly Asp Glu Gly Ala Glu Ala Pro Val Glu
65          70          75          80
Gly Asp Ile His Tyr Gln Arg Gly Ser Gly Ala Pro Leu Pro Pro Ser
85          90          95
Gly Ser Lys Asp Gln Val Gly Gly Gly Gly Glu Phe Gly Gly His Asp
100         105         110
Lys Pro Lys Ile Thr Ala Trp Glu Ala Gly Trp Asn Val Thr Asn Ala
115         120         125
Ile Gln Gly Met Phe Val Leu Gly Leu Pro Tyr Ala Ile Leu His Gly
130         135         140
Gly Tyr Leu Gly Leu Phe Leu Ile Ile Phe Ala Ala Val Val Cys Cys
145         150         155         160
Tyr Thr Gly Lys Ile Leu Ile Ala Cys Leu Tyr Glu Glu Asn Glu Asp
165         170         175
Gly Glu Val Val Arg Val Arg Asp Ser Tyr Val Ala Ile Ala Asn Ala
180         185         190
Cys Cys Ala Pro Arg Phe Pro Thr Leu Gly Gly Arg Val Val Asn Val
195         200         205
Ala Gln Ile Ile Glu Leu Val Met Thr Cys Ile Leu Tyr Val Val Val
210         215         220
Ser Gly Asn Leu Met Tyr Asn Ser Phe Pro Gly Leu Pro Val Ser Gln
225         230         235         240
Lys Ser Trp Ser Ile Ile Ala Thr Ala Val Leu Leu Pro Cys Ala Phe
245         250         255
Leu Lys Asn Leu Lys Ala Val Ser Lys Phe Ser Leu Leu Cys Thr Leu
260         265         270
Ala His Phe Val Ile Asn Ile Leu Val Ile Ala Tyr Cys Leu Ser Arg
275         280         285
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290         295         300
Lys Phe Pro Ile Ser Ile Gly Ile Ile Val Phe Ser Tyr Thr Ser Gln

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1				5					10					15			
cct	gag	cct	gct	ggc	cac	acc	gtt	ctg	tgg	atc	ttc	tca	ttg	cta	gtc		
Pro	Glu	Pro	Ala	Gly	His	Thr	Val	Leu	Trp	Ile	Phe	Ser	Leu	Leu	Val	96	
			20					25					30				
cac	gga	gtc	acc	ttt	gtc	ttc	ggg	gtc	ctg	ggc	aat	ggg	ctt	gtg	atc		
His	Gly	Val	Thr	Phe	Val	Phe	Gly	Val	Leu	Gly	Asn	Gly	Leu	Val	Ile	144	
		35					40					45					
tgg	gtg	gct	gga	ttc	cgg	atg	aca	cgc	aca	gtc	aac	acc	atc	tgt	tac		
Trp	Val	Ala	Gly	Phe	Arg	Met	Thr	Arg	Thr	Val	Asn	Thr	Ile	Cys	Tyr	192	
	50					55					60						
ctg	aac	ctg	gcc	cta	gct	gac	ttc	tct	ttc	agt	gcc	atc	cta	cca	ttc		
Leu	Asn	Leu	Ala	Leu	Ala	Asp	Phe	Ser	Phe	Ser	Ala	Ile	Leu	Pro	Phe	240	
65					70					75					80		
cga	atg	gtc	tca	gtc	gcc	atg	aga	gaa	aaa	tgg	cct	ttt	gcg	tca	ttc		
Arg	Met	Val	Ser	Val	Ala	Met	Arg	Glu	Lys	Trp	Pro	Phe	Ala	Ser	Phe	288	

85	90	95	
cta tgt aag tta gtt cat gtt atg ata gac atc aac ctg ttt gtc agt			336
Leu Cys Lys Leu Val His Val Met Ile Asp Ile Asn Leu Phe Val Ser			
100	105	110	
gtc tac ctg atc acc atc att gct ctg gac cgc tgt att tgt gtc ctg			384
Val Tyr Leu Ile Thr Ile Ile Ala Leu Asp Arg Cys Ile Cys Val Leu			
115	120	125	
cat cca gcc tgg gcc cag aac cat cgc acc atg agt ctg gcc aag agg			432
His Pro Ala Trp Ala Gln Asn His Arg Thr Met Ser Leu Ala Lys Arg			
130	135	140	
gtg atg acg gga ctc tgg att ttc acc ata gtc ctt acc tta cca aat			480
Val Met Thr Gly Leu Trp Ile Phe Thr Ile Val Leu Thr Leu Pro Asn			
145	150	155	160
ttc atc ttc tgg act aca ata agt act acg aat ggg gac aca tac tgt			528
Phe Ile Phe Trp Thr Thr Ile Ser Thr Thr Asn Gly Asp Thr Tyr Cys			
165	170	175	
att ttc aac ttt gca ttc tgg ggt gac act gct gta gag agg ttg aac			576
Ile Phe Asn Phe Ala Phe Trp Gly Asp Thr Ala Val Glu Arg Leu Asn			
180	185	190	
gtg ttc att acc atg gcc aag gtc ttt ctg atc ctc cac ttc att att			624
Val Phe Ile Thr Met Ala Lys Val Phe Leu Ile Leu His Phe Ile Ile			
195	200	205	
ggc ttc acg gtg cct atg tcc atc atc aca gtc tgc tat ggg atc atc			672
Gly Phe Thr Val Pro Met Ser Ile Ile Thr Val Cys Tyr Gly Ile Ile			
210	215	220	
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Ala Ala Lys Ile His Arg Asn His Met Ile Lys Ser Ser Arg Pro Leu			
225	230	235	240
cgt gtc ttc gct gct gtg gtg gct tct ttc ttc atc tgt tgg ttc cct			768
Arg Val Phe Ala Val Val Ala Ser Phe Phe Ile Cys Trp Phe Pro			
245	250	255	
tat gaa cta att ggc att cta atg gca gtc tgg ctc aaa gag atg ttg			816
Tyr Glu Leu Ile Gly Ile Leu Met Ala Val Trp Leu Lys Glu Met Leu			
260	265	270	
tta aat ggc aaa tac aaa atc att ctt gtc ctg att aac cca aca agc			864
Leu Asn Gly Lys Tyr Lys Ile Ile Leu Val Leu Ile Asn Pro Thr Ser			
275	280	285	
tcc ttg gcc ttt ttt aac agc tgc ctc aac cca att ctc tac gtc ttt			912
Ser Leu Ala Phe Phe Asn Ser Cys Leu Asn Pro Ile Leu Tyr Val Phe			
290	295	300	
atg ggt cgt aac ttc caa gaa aga ctg att cgc tct ttg ccc act agt			960
Met Gly Arg Asn Phe Gln Glu Arg Leu Ile Arg Ser Leu Pro Thr Ser			
305	310	315	320
ttg gag agg gcc ctg act gag gtc cct gac tca gcc cag acc agc aac			1008
Leu Glu Arg Ala Leu Thr Glu Val Pro Asp Ser Ala Gln Thr Ser Asn			
325	330	335	



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 His Gly Val Thr Phe Val Phe Gly Val Leu Gly Asn Gly Leu Val Ile  
 35 40 45  
 Trp Val Ala Gly Phe Arg Met Thr Arg Thr Val Asn Thr Ile Cys Tyr  
 50 55 60  
 Leu Asn Leu Ala Leu Ala Asp Phe Ser Phe Ser Ala Ile Leu Pro Phe  
 65 70 75 80  
 Arg Met Val Ser Val Ala Met Arg Glu Lys Trp Pro Phe Ala Ser Phe  
 85 90 95  
 Leu Cys Lys Leu Val His Val Met Ile Asp Ile Asn Leu Phe Val Ser  
 100 105 110  
 Val Tyr Leu Ile Thr Ile Ile Ala Leu Asp Arg Cys Ile Cys Val Leu  
 115 120 125  
 His Pro Ala Trp Ala Gln Asn His Arg Thr Met Ser Leu Ala Lys Arg  
 130 135 140  
 Val Met Thr Gly Leu Trp Ile Phe Thr Ile Val Leu Thr Leu Pro Asn  
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 165 170 175  
 Ile Phe Asn Phe Ala Phe Trp Gly Asp Thr Ala Val Glu Arg Leu Asn  
 180 185 190  
 Val Phe Ile Thr Met Ala Lys Val Phe Leu Ile Leu His Phe Ile Ile  
 195 200 205  
 Gly Phe Thr Val Pro Met Ser Ile Ile Thr Val Cys Tyr Gly Ile Ile  
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 Ala Ala Lys Ile His Arg Asn His Met Ile Lys Ser Ser Arg Pro Leu  
 225 230 235 240  
 Arg Val Phe Ala Ala Val Val Ala Ser Phe Phe Ile Cys Trp Phe Pro  
 245 250 255  
 Tyr Glu Leu Ile Gly Ile Leu Met Ala Val Trp Leu Lys Glu Met Leu  
 260 265 270  
 Leu Asn Gly Lys Tyr Lys Ile Ile Leu Val Leu Ile Asn Pro Thr Ser  
 275 280 285  
 Ser Leu Ala Phe Phe Asn Ser Cys Leu Asn Pro Ile Leu Tyr Val Phe  
 290 295 300  
 Met Gly Arg Asn Phe Gln Glu Arg Leu Ile Arg Ser Leu Pro Thr Ser  
 305 310 315 320  
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 325 330 335  
 Thr His Thr Thr Ser Ala Ser Pro Pro Glu Glu Thr Glu Leu Gln Ala  
 340 345 350  
 Met



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acg cct tac tgg atg gcc ccc gag gtg gtc atg tgt gag acc atg aaa Thr Pro Tyr Trp Met Ala Pro Glu Val Val Met Cys Glu Thr Met Lys 195 200 205 210	680
gac acg ccc tac gac tac aaa gcc gac atc tgg tcc ctg ggc atc acg Asp Thr Pro Tyr Asp Tyr Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr 215 220 225	728
ctg att gag atg gcc cag atc gag ccg cca cac cac gag ctg aac ccc Leu Ile Glu Met Ala Gln Ile Glu Pro Pro His His Glu Leu Asn Pro 230 235 240	776
atg cgg gtc ctg cta aag atc gcc aag tca gac cct ccc acg ctg ctg Met Arg Val Leu Leu Lys Ile Ala Lys Ser Asp Pro Pro Thr Leu Leu 245 250 255	824
acg ccc tcc aag tgg tct gta gag ttc cgt gac ttc ctg aag ata gcc Thr Pro Ser Lys Trp Ser Val Glu Phe Arg Asp Phe Leu Lys Ile Ala 260 265 270	872
ctg gat aag aac cca gaa acc cga ccc agt gcc gcg cag ctg ctg gag Leu Asp Lys Asn Pro Glu Thr Arg Pro Ser Ala Ala Gln Leu Leu Glu 275 280 285 290	920
cat ccc ttc gtc agc agc atc acc agt aac aag gct ctg cgg gag ctg His Pro Phe Val Ser Ser Ile Thr Ser Asn Lys Ala Leu Arg Glu Leu 295 300 305	968
gtg gct gag gcc aag gcc gag gtg atg gaa gag atc gaa gac ggc cgg Val Ala Glu Ala Lys Ala Glu Val Met Glu Glu Ile Glu Asp Gly Arg 310 315 320	1016
gat gag ggg gaa gag gag gac gcc gtg gat gcc gcc tcc acc ctg gag Asp Glu Gly Glu Glu Glu Asp Ala Val Asp Ala Ala Ser Thr Leu Glu 325 330 335	1064
aac cat act cag aac tcc tct gag gtg agt ccg cca agc ctg aat gct Asn His Thr Gln Asn Ser Ser Glu Val Ser Pro Pro Ser Leu Asn Ala 340 345 350	1112
gac aag cct ctg gag gag tca cct tcc acc ccg ctg gca ccc agc cag Asp Lys Pro Leu Glu Glu Ser Pro Ser Thr Pro Leu Ala Pro Ser Gln 355 360 365 370	1160
tct cag gac agt gtg aat gag ccc tgc agc cag ccc tct ggg gac aga Ser Gln Asp Ser Val Asn Glu Pro Cys Ser Gln Pro Ser Gly Asp Arg 375 380 385	1208
tcc ctg caa acc acc agt ccc cca gtc gtg gcc cct gga aat gag aac Ser Leu Gln Thr Thr Ser Pro Pro Val Val Ala Pro Gly Asn Glu Asn 390 395 400	1256
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Asp	Ala	Arg	Ile	Gln	Val	Ala	Gln	Glu	Lys	Gln	Val	Ala	Glu	Gln	Gly		
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Gly	Asp	Leu	Ser	Pro	Ala	Ala	Asn	Arg	Ser	Gln	Lys	Ala	Ser	Gln	Ser		
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Arg	Pro	Asn	Ser	Ser	Ala	Leu	Glu	Thr	Leu	Gly	Gly	Glu	Lys	Leu	Ala		
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aat	ggc	agc	ctg	gag	cca	cct	gcc	cag	gca	gct	cca	ggg	cct	tcc	aag	1496	
Asn	Gly	Ser	Leu	Glu	Pro	Pro	Ala	Gln	Ala	Ala	Pro	Gly	Pro	Ser	Lys		
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agg	gac	tcg	gac	tgc	agc	agc	ctc	tgc	acc	tct	gag	agc	atg	gac	tat	1544	
Arg	Asp	Ser	Asp	Cys	Ser	Ser	Leu	Cys	Thr	Ser	Glu	Ser	Met	Asp	Tyr		
	485						490					495					
ggg	acc	aat	ctc	tcc	act	gac	ctg	tcg	ctg	aac	aaa	gag	atg	ggc	tct	1592	
Gly	Thr	Asn	Leu	Ser	Thr	Asp	Leu	Ser	Leu	Asn	Lys	Glu	Met	Gly	Ser		
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Leu	Ser	Ile	Lys	Asp	Pro	Lys	Leu	Tyr	Lys	Lys	Thr	Leu	Lys	Arg	Thr		
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cgc	aaa	ttt	gtg	gtg	gat	ggg	gtg	gag	gtg	agc	atc	acc	acc	tcc	aag	1688	
Arg	Lys	Phe	Val	Val	Asp	Gly	Val	Glu	Val	Ser	Ile	Thr	Thr	Ser	Lys		
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atc	atc	agc	gaa	gat	gag	aag	aag	gat	gag	gag	atg	aga	ttt	ctc	agg	1736	
Ile	Ile	Ser	Glu	Asp	Glu	Lys	Lys	Asp	Glu	Glu	Met	Arg	Phe	Leu	Arg		
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Asn	Gln	Thr	Gln	Leu	Ser	Asn	Lys	His	Glu	Leu	Gln	Leu	Glu	Gln	Met		
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cat	aaa	cgt	ttt	gaa	cag	gaa	atc	aac	gcc	aag	aag	aag	ttc	ttt	gac	1880	
His	Lys	Arg	Phe	Glu	Gln	Glu	Ile	Asn	Ala	Lys	Lys	Lys	Phe	Phe	Asp		
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Met	Glu	Gln	Asp	His	Ala	Val	Arg	Arg	Arg	Glu	Glu	Ala	Arg	Arg	Ile		
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cgc	ctg	gag	cag	gat	cgg	gac	tac	acc	agg	ttc	caa	gag	cag	ctc	aaa	2024	
Arg	Leu	Glu	Gln	Asp	Arg	Asp	Tyr	Thr	Arg	Phe	Gln	Glu	Gln	Leu	Lys		
		645				650					655						
ctg	atg	aag	aaa	gag	gtg	aag	aac	gag	gtg	gag	aag	ctc	ccc	cga	cag	2072	
Leu	Met	Lys	Lys	Glu	Val	Lys	Asn	Glu	Val	Glu	Lys	Leu	Pro	Arg	Gln		

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Gln Arg Lys Glu Ser Met Lys Gln Lys Met Glu Glu His Thr Gln Lys			
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Lys Gln Leu Leu Asp Arg Asp Phe Val Ala Lys Gln Lys Glu Asp Leu			
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gag ctg gcc atg aag agg ctc acc acc gac aac agg cgg gag atc tgt			2216
Glu Leu Ala Met Lys Arg Leu Thr Thr Asp Asn Arg Arg Glu Ile Cys			
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Asp Lys Glu Arg Glu Cys Leu Met Lys Lys Gln Glu Leu Leu Arg Asp			
	725	730	735
cgg gaa gca gcc ctg tgg gag atg gaa gag cac cag ctg cag gag agg			2312
Arg Glu Ala Ala Leu Trp Glu Met Glu Glu His Gln Leu Gln Glu Arg			
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cac cag ctg gtg aag cag cag ctc aaa gac cag tac ttc ctc cag cgg			2360
His Gln Leu Val Lys Gln Gln Leu Lys Asp Gln Tyr Phe Leu Gln Arg			
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cac gag ctg ctg cgc aag cat gag aag gag cgg gag cag atg cag cgc			2408
His Glu Leu Leu Arg Lys His Glu Lys Glu Arg Glu Gln Met Gln Arg			
	775	780	785
tac aac cag cgc atg ata gag cag ctg aag gtg cgg cag caa cag gaa			2456
Tyr Asn Gln Arg Met Ile Glu Gln Leu Lys Val Arg Gln Gln Gln Glu			
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Lys Ala Arg Leu Pro Lys Ile Gln Arg Ser Glu Gly Lys Thr Arg Met			
	805	810	815
gcc atg tac aag aag agc ctc cac atc aac ggc ggc ggc agc gca gct			2552
Ala Met Tyr Lys Lys Ser Leu His Ile Asn Gly Gly Gly Ser Ala Ala			
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Glu Gln Arg Glu Lys Ile Lys Gln Phe Ser Gln Gln Glu Glu Lys Arg			
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Gln Lys Ser Glu Arg Leu Gln Gln Gln Gln Lys His Glu Asn Gln Met			
	855	860	865
cgg gac atg ctg gcg cag tgt gag agc aac atg agc gag ctg cag cag			2696
Arg Asp Met Leu Ala Gln Cys Glu Ser Asn Met Ser Glu Leu Gln Gln			
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Leu Lys Ala Leu Asp Glu Ser His Asn Gln Asn Leu Lys Glu Trp Arg			
	900	905	910

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 935 940 945  
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 Cys Pro Asn Pro Ser Thr Pro Ser Lys Ala Ala Lys Phe Phe Pro Tyr  
 950 955 960  
 agt tct gcg gat gct tct taa caaccgcccg gggctgtggc tggcagcttg 2987  
 Ser Ser Ala Asp Ala Ser \*  
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 35 40 45  
 Lys Val Tyr Lys Ala Lys Asn Lys Glu Thr Gly Ala Leu Ala Ala Ala  
 50 55 60  
 Lys Val Ile Glu Thr Lys Ser Glu Glu Glu Leu Glu Asp Tyr Ile Val  
 65 70 75 80  
 Glu Ile Glu Ile Leu Ala Thr Cys Asp His Pro Tyr Ile Val Lys Leu  
 85 90 95  
 Leu Gly Ala Tyr Tyr His Asp Gly Lys Leu Trp Ile Met Ile Glu Phe  
 100 105 110  
 Cys Pro Gly Gly Ala Val Asp Ala Ile Met Leu Glu Leu Asp Arg Gly  
 115 120 125

Leu Thr Glu Pro Gln Ile Gln Val Val Cys Arg Gln Met Leu Glu Ala  
 130 135 140  
 Leu Asn Phe Leu His Ser Lys Arg Ile Ile His Arg Asp Leu Lys Ala  
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 Gly Asn Val Leu Met Thr Leu Glu Gly Asp Ile Arg Leu Ala Asp Phe  
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 Gly Val Ser Ala Lys Asn Leu Lys Thr Leu Gln Lys Arg Asp Ser Phe  
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 Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Val Met Cys Glu Thr  
 195 200 205  
 Met Lys Asp Thr Pro Tyr Asp Tyr Lys Ala Asp Ile Trp Ser Leu Gly  
 210 215 220  
 Ile Thr Leu Ile Glu Met Ala Gln Ile Glu Pro Pro His His Glu Leu  
 225 230 235 240  
 Asn Pro Met Arg Val Leu Leu Lys Ile Ala Lys Ser Asp Pro Pro Thr  
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 Leu Leu Thr Pro Ser Lys Trp Ser Val Glu Phe Arg Asp Phe Leu Lys  
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 Ile Ala Leu Asp Lys Asn Pro Glu Thr Arg Pro Ser Ala Ala Gln Leu  
 275 280 285  
 Leu Glu His Pro Phe Val Ser Ser Ile Thr Ser Asn Lys Ala Leu Arg  
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 Glu Leu Val Ala Glu Ala Lys Ala Glu Val Met Glu Glu Ile Glu Asp  
 305 310 315 320  
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 Asp Arg Ser Leu Gln Thr Thr Ser Pro Pro Val Val Ala Pro Gly Asn  
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 Ser Met Asp Ala Arg Ile Gln Val Ala Gln Glu Lys Gln Val Ala Glu  
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 Ser Lys Arg Asp Ser Asp Cys Ser Ser Leu Cys Thr Ser Glu Ser Met  
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 His Arg Asn Gln Thr Gln Leu Ser Asn Lys His Glu Leu Gln Leu Glu  
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 Gln Met His Lys Arg Phe Glu Gln Glu Ile Asn Ala Lys Lys Lys Phe  
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 Phe Asp Thr Glu Leu Glu Asn Leu Glu Arg Gln Gln Lys Gln Gln Val

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Arg Ile Arg Leu Glu Gln Asp	Arg Asp Tyr Thr Arg	Phe Gln Glu Glu
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Leu Lys Leu Met Lys Lys	Glu Val Lys Asn Glu Val	Glu Lys Leu Pro
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Arg Gln Gln Arg Lys Glu Ser	Met Lys Gln Lys Met	Glu Glu His Thr
675	680	685
Gln Lys Lys Gln Leu Leu Asp	Arg Asp Phe Val Ala	Lys Gln Lys Glu
690	695	700
Asp Leu Glu Leu Ala Met Lys	Arg Leu Thr Thr Asp	Asn Arg Arg Glu
705	710	715
Ile Cys Asp Lys Glu Arg Glu	Cys Leu Met Lys Lys	Gln Glu Leu Leu
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Arg Asp Arg Glu Ala Ala Leu	Trp Glu Met Glu Glu	His Gln Leu Gln
740	745	750
Glu Arg His Gln Leu Val Lys	Gln Gln Leu Lys Asp	Gln Tyr Phe Leu
755	760	765
Gln Arg His Glu Leu Leu Arg	Lys His Glu Lys Glu	Arg Glu Gln Met
770	775	780
Gln Arg Tyr Asn Gln Arg Met	Ile Glu Gln Leu Lys	Val Arg Gln Gln
785	790	795
Gln Glu Lys Ala Arg Leu Pro	Lys Ile Gln Arg Ser	Glu Gly Lys Thr
805	810	815
Arg Met Ala Met Tyr Lys Lys	Ser Leu His Ile Asn	Gly Gly Gly Ser
820	825	830
Ala Ala Glu Gln Arg Glu Lys	Ile Lys Gln Phe Ser	Gln Gln Glu Glu
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Lys Arg Gln Lys Ser Glu Arg	Leu Gln Gln Gln Lys	His Glu Asn
850	855	860
Gln Met Arg Asp Met Leu Ala	Gln Cys Glu Ser Asn	Met Ser Glu Leu
865	870	875
Gln Gln Leu Gln Asn Glu Lys	Cys His Leu Leu Val	Glu His Glu Thr
885	890	895
Gln Lys Leu Lys Ala Leu Asp	Glu Ser His Asn Gln	Asn Leu Lys Glu
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Trp Arg Asp Lys Leu Arg Pro	Arg Lys Lys Ala Leu	Glu Glu Asp Leu
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Asn Gln Lys Lys Arg Glu Gln	Glu Met Phe Phe Lys	Leu Ser Glu Glu
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Pro Tyr Ser Ser Ala Asp	Ala Ser	
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Met Tyr Phe Cys Trp Gly Ala Asp Ser Arg  
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Cys His Lys Gly Arg Val Phe Ala Trp Gly Ala Gly Ser Glu Gly Gln	
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Leu Gly Ile Gly Glu Phe Lys Glu Ile Ser Phe Thr Pro Lys Lys Ile	
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Met Thr Leu Asn Asp Ile Lys Ile Ile Gln Val Ser Cys Gly His Tyr	
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His Ser Leu Ala Leu Ser Lys Asp Ser Gln Val Phe Ser Trp Gly Lys	
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 His Gln Glu Ala Leu Ser Val Phe Leu Leu Leu Pro Glu Cys Pro Val  
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tgg gca ttt ttg caa gaa tct tct ctg aat ccg ctg atc cag atg ctt	1695
Trp Ala Phe Leu Gln Glu Ser Ser Leu Asn Pro Leu Ile Gln Met Leu	
525 530 535	
aaa gca gcc atc atc tct cag ctg ctt cat cag act aaa acc gaa cag	1743
Lys Ala Ala Ile Ile Ser Gln Leu Leu His Gln Thr Lys Thr Glu Gln	
540 545 550	
gat cac tgt aat gtt aaa gct ctt tta gga atg atg aaa gaa ctg cat	1791
Asp His Cys Asn Val Lys Ala Leu Leu Gly Met Met Lys Glu Leu His	
555 560 565 570	
aag gta aac aaa gct aac tgt cga cta cca gaa aat act ttc aac ata	1839
Lys Val Asn Lys Ala Asn Cys Arg Leu Pro Glu Asn Thr Phe Asn Ile	
575 580 585	
aat gaa ctc tcc aac tta tta aac ttt tat ata gat aga gga aga cag	1887
Asn Glu Leu Ser Asn Leu Leu Asn Phe Tyr Ile Asp Arg Gly Arg Gln	
590 595 600	
ctc ttt cgg gat aac cac ctg ata cct gca gaa acc ccc agt cct gtt	1935
Leu Phe Arg Asp Asn His Leu Ile Pro Ala Glu Thr Pro Ser Pro Val	
605 610 615	
att ttc agt gat ttt cca ttt atc ttt aat tcg cta tcc aaa att aaa	1983
Ile Phe Ser Asp Phe Pro Phe Ile Phe Asn Ser Leu Ser Lys Ile Lys	
620 625 630	
tta ttg caa gct gat tca cat ata aag atg cag atg tca gaa aag aaa	2031
Leu Leu Gln Ala Asp Ser His Ile Lys Met Gln Met Ser Glu Lys Lys	
635 640 645 650	
gca tac atg ctt atg cat gaa aca att ctg caa aaa aag gat gaa ttt	2079
Ala Tyr Met Leu Met His Glu Thr Ile Leu Gln Lys Lys Asp Glu Phe	
655 660 665	
cct cca tca ccc aga ttt ata ctt aga gtc aga cga agt cgc ctg gtt	2127
Pro Pro Ser Pro Arg Phe Ile Leu Arg Val Arg Arg Ser Arg Leu Val	
670 675 680	
aaa gat gct ctg cgt caa tta agt caa gct gaa gct act gac ttc tgc	2175
Lys Asp Ala Leu Arg Gln Leu Ser Gln Ala Glu Ala Thr Asp Phe Cys	
685 690 695	
aaa gta tta gtg gtt gaa ttt att aat gaa att tgt cct gag tct gga	2223
Lys Val Leu Val Val Glu Phe Ile Asn Glu Ile Cys Pro Glu Ser Gly	
700 705 710	
ggg gtt agt tca gag ttc ttc cac tgt atg ttt gaa gag atg acc aag	2271
Gly Val Ser Ser Glu Phe Phe His Cys Met Phe Glu Glu Met Thr Lys	
715 720 725 730	
cca gaa tat gga atg ttc atg tat cct gaa atg ggt tcc tgc atg tgg	2319
Pro Glu Tyr Gly Met Phe Met Tyr Pro Glu Met Gly Ser Cys Met Trp	

735	740	745	
ttt cct gcc aag cct aaa cct gag aag aaa aga tat ttc ctc ttt gga			2367
Phe Pro Ala Lys Pro Lys Pro Glu Lys Lys Arg Tyr Phe Leu Phe Gly			
750	755	760	
atg ctg tgt gga ctc tcc tta ttc aat tta aat gtt gct aac ctt cct			2415
Met Leu Cys Gly Leu Ser Leu Phe Asn Leu Asn Val Ala Asn Leu Pro			
765	770	775	
ttc cca ctg gct ctg tat aaa aaa ctt ctg gac caa aag cca tca ttg			2463
Phe Pro Leu Ala Leu Tyr Lys Lys Leu Leu Asp Gln Lys Pro Ser Leu			
780	785	790	
gaa gat tta aaa gaa ctc agt cct cgg ttg ggg aag agt ttg caa gaa			2511
Glu Asp Leu Lys Glu Leu Ser Pro Arg Leu Gly Lys Ser Leu Gln Glu			
795	800	805	810
gtt cta gat gat gct gct gat gac att gga gat gcg ctc tgc ata cgc			2559
Val Leu Asp Asp Ala Ala Asp Asp Ile Gly Asp Ala Leu Cys Ile Arg			
815	820	825	
ttt tct ata cac tgg gac caa aat gat gtt gac tta att cca aat ggg			2607
Phe Ser Ile His Trp Asp Gln Asn Asp Val Asp Leu Ile Pro Asn Gly			
830	835	840	
atc tcc ata cct gtg gac caa acc aac aag aga gac tat gtt tct aag			2655
Ile Ser Ile Pro Val Asp Gln Thr Asn Lys Arg Asp Tyr Val Ser Lys			
845	850	855	
tat att gat tac att ttc aac gtc tct gta aaa gca gtt tat gag gaa			2703
Tyr Ile Asp Tyr Ile Phe Asn Val Ser Val Lys Ala Val Tyr Glu Glu			
860	865	870	
ttt cag aga gga ttt tat aga gtc tgt gag aag gag ata ctt aga cat			2751
Phe Gln Arg Gly Phe Tyr Arg Val Cys Glu Lys Glu Ile Leu Arg His			
875	880	885	890
ttc tac cct gaa gaa cta atg aca gca atc att gga aat act gat tat			2799
Phe Tyr Pro Glu Glu Leu Met Thr Ala Ile Ile Gly Asn Thr Asp Tyr			
895	900	905	
gac tgg aaa cag ttt gaa cag aat tca aag tat gag caa gga tac caa			2847
Asp Trp Lys Gln Phe Glu Gln Asn Ser Lys Tyr Glu Gln Gly Tyr Gln			
910	915	920	
aaa tca cat cct act ata cag ttg ttt tgg aag gct ttc cac aaa cta			2895
Lys Ser His Pro Thr Ile Gln Leu Phe Trp Lys Ala Phe His Lys Leu			
925	930	935	
acc ttg gat gaa aag aaa aaa ttc ctc ttt ttc ctt aca gga cgt gat			2943
Thr Leu Asp Glu Lys Lys Lys Phe Leu Phe Phe Leu Thr Gly Arg Asp			
940	945	950	
agg ctg cat gca aga ggc ata cag aaa atg gaa ata gta ttt cgc tgt			2991
Arg Leu His Ala Arg Gly Ile Gln Lys Met Glu Ile Val Phe Arg Cys			
955	960	965	970
cct gaa act ttc agt gaa aga gat cac cca aca tca ata act tgt cat			3039
Pro Glu Thr Phe Ser Glu Arg Asp His Pro Thr Ser Ile Thr Cys His			
975	980	985	

aat att ctc tcc ctc cct aag tat tct aca atg gaa aga atg gag gaa 3087  
 Asn Ile Leu Ser Leu Pro Lys Tyr Ser Thr Met Glu Arg Met Glu Glu  
                   . 990                                  995                                  1000

gca ctt caa gta gcc atc aac aac aac aga gga ttt gtc tca ccc atg 3135  
 Ala Leu Gln Val Ala Ile Asn Asn Asn Arg Gly Phe Val Ser Pro Met  
                   1005                                  1010                                  1015

ctc aca cag tca taa tcacctctga gagactcagg gtgggctttc tcacacttgg 3190  
 Leu Thr Gln Ser \*  
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atccttctgt tcttccttac acctaaataa tacaagagat taatgaatag tggttagaag 3250  
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<213> Homo sapiens

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                                   20                                  25                                  30  
 Arg His Ser Leu Leu Leu Leu Thr Asn His Arg Val Leu Ser Cys Gly  
                                   35                                  40                                  45  
 Asp Asn Ser Arg Gly Gln Leu Gly Arg Arg Gly Ala Gln Arg Gly Glu  
                                   50                                  55                                  60  
 Leu Pro Glu Pro Ile Gln Ala Leu Glu Thr Leu Ile Val Asp Leu Val  
                                   65                                  70                                  75                                  80  
 Ser Cys Gly Lys Glu His Ser Leu Ala Val Cys His Lys Gly Arg Val  
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 Phe Ala Trp Gly Ala Gly Ser Glu Gly Gln Leu Gly Ile Gly Glu Phe  
                                   100                                  105                                  110  
 Lys Glu Ile Ser Phe Thr Pro Lys Lys Ile Met Thr Leu Asn Asp Ile  
                                   115                                  120                                  125  
 Lys Ile Ile Gln Val Ser Cys Gly His Tyr His Ser Leu Ala Leu Ser  
                                   130                                  135                                  140  
 Lys Asp Ser Gln Val Phe Ser Trp Gly Lys Asn Ser His Gly Gln Leu  
                                   145                                  150                                  155                                  160  
 Gly Leu Gly Lys Glu Phe Pro Ser Gln Ala Ser Pro Gln Arg Val Arg  
                                   165                                  170                                  175  
 Ser Leu Glu Gly Ile Pro Leu Ala Gln Val Ala Ala Gly Gly Ala His  
                                   180                                  185                                  190  
 Ser Phe Ala Leu Ser Leu Cys Gly Thr Ser Phe Gly Trp Gly Ser Asn  
                                   195                                  200                                  205  
 Ser Ala Gly Gln Leu Ala Leu Ser Gly Arg Asn Val Pro Val Gln Ser  
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 Asn Lys Pro Leu Ser Val Gly Ala Leu Lys Asn Leu Gly Val Val Tyr  
                                   225                                  230                                  235                                  240  
 Ile Ser Cys Gly Asp Ala His Thr Ala Val Leu Thr Gln Asp Gly Lys  
                                   245                                  250                                  255  
 Val Phe Thr Phe Gly Asp Asn Arg Ser Gly Gln Leu Gly Tyr Ser Pro  
                                   260                                  265                                  270  
 Thr Pro Glu Lys Arg Gly Pro Gln Leu Val Glu Arg Ile Asp Gly Leu

275	280	285
Val Ser Gln Ile Asp Cys Gly	Ser Tyr His Thr Leu Ala Tyr Val His	
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Thr Thr Gly Gln Val Val Ser Phe Gly His Gly Pro Ser Asp Thr Ser		
305	310	315
Lys Pro Thr His Pro Glu Ala Leu Thr Glu Asn Phe Asp Ile Ser Cys		
325	330	335
Leu Ile Ser Ala Glu Asp Phe Val Asp Val Gln Val Lys His Ile Phe		
340	345	350
Ala Gly Thr Tyr Ala Asn Phe Val Thr Thr His Gln Asp Thr Ser Ser		
355	360	365
Thr Arg Ala Pro Gly Lys Thr Leu Pro Glu Ile Ser Arg Ile Ser Gln		
370	375	380
Ser Met Ala Glu Lys Trp Ile Ala Val Lys Arg Arg Ser Thr Glu His		
385	390	395
Glu Met Ala Lys Ser Glu Ile Arg Met Ile Phe Ser Ser Pro Ala Cys		
405	410	415
Leu Thr Ala Ser Phe Leu Lys Lys Arg Gly Thr Gly Glu Thr Thr Ser		
420	425	430
Ile Asp Val Asp Leu Glu Met Ala Arg Asp Thr Phe Lys Lys Leu Thr		
435	440	445
Lys Lys Glu Trp Ile Ser Ser Met Ile Thr Thr Cys Leu Glu Asp Asp		
450	455	460
Leu Leu Arg Ala Leu Pro Cys His Ser Pro His Gln Glu Ala Leu Ser		
465	470	475
Val Phe Leu Leu Leu Pro Glu Cys Pro Val Met His Asp Ser Lys Asn		
485	490	495
Trp Lys Asn Leu Val Val Pro Phe Ala Lys Ala Val Cys Glu Met Ser		
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Lys Gln Ser Leu Gln Val Leu Lys Lys Cys Trp Ala Phe Leu Gln Glu		
515	520	525
Ser Ser Leu Asn Pro Leu Ile Gln Met Leu Lys Ala Ala Ile Ile Ser		
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Gln Leu Leu His Gln Thr Lys Thr Glu Gln Asp His Cys Asn Val Lys		
545	550	555
Ala Leu Leu Gly Met Met Lys Glu Leu His Lys Val Asn Lys Ala Asn		
565	570	575
Cys Arg Leu Pro Glu Asn Thr Phe Asn Ile Asn Glu Leu Ser Asn Leu		
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Leu Asn Phe Tyr Ile Asp Arg Gly Arg Gln Leu Phe Arg Asp Asn His		
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Leu Ile Pro Ala Glu Thr Pro Ser Pro Val Ile Phe Ser Asp Phe Pro		
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Phe Ile Phe Asn Ser Leu Ser Lys Ile Lys Leu Leu Gln Ala Asp Ser		
625	630	635
His Ile Lys Met Gln Met Ser Glu Lys Lys Ala Tyr Met Leu Met His		
645	650	655
Glu Thr Ile Leu Gln Lys Lys Asp Glu Phe Pro Pro Ser Pro Arg Phe		
660	665	670
Ile Leu Arg Val Arg Arg Ser Arg Leu Val Lys Asp Ala Leu Arg Gln		
675	680	685
Leu Ser Gln Ala Glu Ala Thr Asp Phe Cys Lys Val Leu Val Val Glu		
690	695	700
Phe Ile Asn Glu Ile Cys Pro Glu Ser Gly Gly Val Ser Ser Glu Phe		
705	710	715
Phe His Cys Met Phe Glu Glu Met Thr Lys Pro Glu Tyr Gly Met Phe		
725	730	735
Met Tyr Pro Glu Met Gly Ser Cys Met Trp Phe Pro Ala Lys Pro Lys		
740	745	750
Pro Glu Lys Lys Arg Tyr Phe Leu Phe Gly Met Leu Cys Gly Leu Ser		
755	760	765

Leu Phe Asn Leu Asn Val Ala Asn Leu Pro Phe Pro Leu Ala Leu Tyr  
 770 775 780  
 Lys Lys Leu Leu Asp Gln Lys Pro Ser Leu Glu Asp Leu Lys Glu Leu  
 785 790 795 800  
 Ser Pro Arg Leu Gly Lys Ser Leu Gln Glu Val Leu Asp Asp Ala Ala  
 805 810 815  
 Asp Asp Ile Gly Asp Ala Leu Cys Ile Arg Phe Ser Ile His Trp Asp  
 820 825 830  
 Gln Asn Asp Val Asp Leu Ile Pro Asn Gly Ile Ser Ile Pro Val Asp  
 835 840 845  
 Gln Thr Asn Lys Arg Asp Tyr Val Ser Lys Tyr Ile Asp Tyr Ile Phe  
 850 855 860  
 Asn Val Ser Val Lys Ala Val Tyr Glu Glu Phe Gln Arg Gly Phe Tyr  
 865 870 875 880  
 Arg Val Cys Glu Lys Glu Ile Leu Arg His Phe Tyr Pro Glu Glu Leu  
 885 890 895  
 Met Thr Ala Ile Ile Gly Asn Thr Asp Tyr Asp Trp Lys Gln Phe Glu  
 900 905 910  
 Gln Asn Ser Lys Tyr Glu Gln Gly Tyr Gln Lys Ser His Pro Thr Ile  
 915 920 925  
 Gln Leu Phe Trp Lys Ala Phe His Lys Leu Thr Leu Asp Glu Lys Lys  
 930 935 940  
 Lys Phe Leu Phe Phe Leu Thr Gly Arg Asp Arg Leu His Ala Arg Gly  
 945 950 955 960  
 Ile Gln Lys Met Glu Ile Val Phe Arg Cys Pro Glu Thr Phe Ser Glu  
 965 970 975  
 Arg Asp His Pro Thr Ser Ile Thr Cys His Asn Ile Leu Ser Leu Pro  
 980 985 990  
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 ccatgagccc ctccgcgact cggcgctgag cccgccaccg gtccagcgcc ccaggaccgg 180  
 ccgcccggctg ccggcttgcc gaagccccct caggatcccc tcaacaagg atg gaa ctg 238  
 Met Glu Leu  
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aag gcc gag gag gag gag gtg ggt ggc gtc cag ccg gtg agc atc cag 286  
 Lys Ala Glu Glu Glu Glu Val Gly Gly Val Gln Pro Val Ser Ile Gln  
 5 10 15

gcc ttc gcc agc agc tcc aca ctg cac ggc ctg gcc cac atc ttc tcc 334  
 Ala Phe Ala Ser Ser Thr Leu His Gly Leu Ala His Ile Phe Ser  
 20 25 30 35

tac gag cgg ctg tct ctg aag cgg gca ctg tgg gcc ctg tgc ttc ctg 382

Tyr Glu Arg Leu Ser Leu Lys Arg Ala Leu Trp Ala Leu Cys Phe Leu  
                                     40                                    45                                    50

ggc tgc ctg gct gtg ctg ctg tgt gtg tgc acg gag cgt gtg cag tac 430  
 Gly Ser Leu Ala Val Leu Leu Cys Val Cys Thr Glu Arg Val Gln Tyr  
                                     55                                    60                                    65

tac ttc cac tac cac cat gtc acc aag ctc gac gag gtg gct gcc tct 478  
 Tyr Phe His Tyr His His Val Thr Lys Leu Asp Glu Val Ala Ala Ser  
                                     70                                    75                                    80

cag ctt acc ttc cct gct gtc acg ctg tgc aac ctc aac gag ttc cgc 526  
 Gln Leu Thr Phe Pro Ala Val Thr Leu Cys Asn Leu Asn Glu Phe Arg  
                                     85                                    90                                    95

ttt agc caa gtc tcc aag aat gac ctg tat cat gct ggg gag ctg ctg 574  
 Phe Ser Gln Val Ser Lys Asn Asp Leu Tyr His Ala Gly Glu Leu Leu  
 100                                    105                                    110                                    115

gcc ctg ctc aac aac agg tat gag ata cca gac aca cag atg gca gat 622  
 Ala Leu Leu Asn Asn Arg Tyr Glu Ile Pro Asp Thr Gln Met Ala Asp  
                                     120                                    125                                    130

gaa aag cag ctg gag ata ctg cag gac aaa gcc aac ttc cgc agc ttc 670  
 Glu Lys Gln Leu Glu Ile Leu Gln Asp Lys Ala Asn Phe Arg Ser Phe  
                                     135                                    140                                    145

aaa ccc aaa ccc ttc aac atg cgt gag ttc tac gac cga gct ggg cac 718  
 Lys Pro Lys Pro Phe Asn Met Arg Glu Phe Tyr Asp Arg Ala Gly His  
                                     150                                    155                                    160

gac att cga gac atg ctg ctc tcc tgc cac ttc cgg ggg gag gtc tgc 766  
 Asp Ile Arg Asp Met Leu Leu Ser Cys His Phe Arg Gly Glu Val Cys  
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agc gct gaa gac ttc aag gtg gtc ttc aca cgc tat gga aag tgc tac 814  
 Ser Ala Glu Asp Phe Lys Val Val Phe Thr Arg Tyr Gly Lys Cys Tyr  
 180                                    185                                    190                                    195

acg ttc aac tgc ggc cga gat ggg cgg ccg cgg ctg aag acc atg aag 862  
 Thr Phe Asn Ser Gly Arg Asp Gly Arg Pro Arg Leu Lys Thr Met Lys  
                                     200                                    205                                    210

gat ggg acg ggc aat ggg ctg gaa atc atg ctg gac atc cag cag gac 910  
 Asp Gly Thr Gly Asn Gly Leu Glu Ile Met Leu Asp Ile Gln Gln Asp  
                                     215                                    220                                    225

gag tac ctg cct gtg tgg ggg gag act gac gag acg tcc ttc gaa gca 958  
 Glu Tyr Leu Pro Val Trp Gly Glu Thr Asp Glu Thr Ser Phe Glu Ala  
                                     230                                    235                                    240

ggc atc aaa gtg cag atc cat agt cag gat gaa cct cct ttc atc gac 1006  
 Gly Ile Lys Val Gln Ile His Ser Gln Asp Glu Pro Pro Phe Ile Asp  
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cag ctg ggc ttt ggc gtg gcc cca ggc ttc cag acc ttt gtg gcc tgc 1054  
 Gln Leu Gly Phe Gly Val Ala Pro Gly Phe Gln Thr Phe Val Ala Cys  
 260                                    265                                    270                                    275

cag gag cag cgg ctc atc tac ctg ccc cca ccc tgg ggc acc tgc aaa 1102  
 Gln Glu Gln Arg Leu Ile Tyr Leu Pro Pro Pro Trp Gly Thr Cys Lys



280										285					290					
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295 300 305																				
act gcc tgc cgc atc gac tgt gag acg cgc tac ctg gtg gag aac tgc	1198																			
Thr Ala Cys Arg Ile Asp Cys Glu Thr Arg Tyr Leu Val Glu Asn Cys																				
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Asn Cys Arg Met Val His Met Pro Gly Asp Ala Pro Tyr Cys Thr Pro																				
325 330 335																				
gag cag tac aag gag tgt gca gat cct gct ctg gac ttc ctg gtg gag	1294																			
Glu Gln Tyr Lys Glu Cys Ala Asp Pro Ala Leu Asp Phe Leu Val Glu																				
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Tyr Gly Lys Glu Leu Ser Met Val Lys Ile Pro Ser Lys Ala Ser Ala																				
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Tyr His Pro Lys Ala Gly Cys Ser Leu Leu Ser His Glu Gly Pro Pro																				
455 460 465																				
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Pro Gln Arg Pro Phe Pro Lys Pro Cys Cys Leu Gly Asp Ile Gly Gly																				
470 475 480																				
cag atg ggg ctg ttc atc ggg gcc agc atc ctc acg gtg ctg gag ctc	1726																			
Gln Met Gly Leu Phe Ile Gly Ala Ser Ile Leu Thr Val Leu Glu Leu																				
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Phe Asp Tyr Ala Tyr Glu Val Ile Lys His Lys Leu Cys Arg Arg Gly																				
500 505 510 515																				
aaa tgc cag aag gag gcc aaa agg agc agt gcg gac aag ggc gtg gcc	1822																			
Lys Cys Gln Lys Glu Ala Lys Arg Ser Ser Ala Asp Lys Gly Val Ala																				
520 525 530																				

ctc agc ctg gac gac gtc aaa aga cac aac ccg tgc gag agc ctt cgg 1870  
 Leu Ser Leu Asp Asp Val Lys Arg His Asn Pro Cys Glu Ser Leu Arg  
                   535                                  540                                  545

ggc cac cct gcc ggg atg aca tac gct gcc aac atc cta cct cac cat 1918  
 Gly His Pro Ala Gly Met Thr Tyr Ala Ala Asn Ile Leu Pro His His  
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ccg gcc cga ggc acg ttc gag gac ttt acc tgc tga gccccgcagg 1964  
 Pro Ala Arg Gly Thr Phe Glu Asp Phe Thr Cys \*  
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 taaggaagga gtcttgacca tagagtccctc tctctgcctc tatcccatc yttttacatt 2144  
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 gttgctgtag agatagcccc caccagggg atggagggtct accctggaca ctaagccaag 3344  
 tgtgtcagag acagaaggga gctggggatt ggcgactcct gaagttgggg cagtgggatg 3404  
 ctgacaggca gaagctgagg tcctcagtca gtggcctttc ctccctctgg gtgcccagcc 3464  
 cccttctctc acctgatacc caagcccacc acttttattt tctggtgagg tgggtttggg 3524  
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 ctgagcccca accctctctc aggccttctc tccttagctg tgtcttggtc ttcaatccca 3704  
 gaacaggacc tgtgagcagc tgcattggcc tggagctgga gagtaaggct gtaggatctt 3764  
 tggaatctct tggttcctaa gagtttctc agagatcata cctccccaga gggaagcagg 3824  
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<211> 574

<212> PRT

<213> Homo sapiens

<400> 18

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 Ser Ile Gln Ala Phe Ala Ser Ser Ser Thr Leu His Gly Leu Ala His  
                   20                                  25                                  30  
 Ile Phe Ser Tyr Glu Arg Leu Ser Leu Lys Arg Ala Leu Trp Ala Leu  
                   35                                  40                                  45  
 Cys Phe Leu Gly Ser Leu Ala Val Leu Leu Cys Val Cys Thr Glu Arg  
                   50                                  55                                  60

Val	Gln	Tyr	Tyr	Phe	His	Tyr	His	His	Val	Thr	Lys	Leu	Asp	Glu	Val
65					70					75					80
Ala	Ala	Ser	Gln	Leu	Thr	Phe	Pro	Ala	Val	Thr	Leu	Cys	Asn	Leu	Asn
				85					90					95	
Glu	Phe	Arg	Phe	Ser	Gln	Val	Ser	Lys	Asn	Asp	Leu	Tyr	His	Ala	Gly
				100				105					110		
Glu	Leu	Leu	Ala	Leu	Leu	Asn	Asn	Arg	Tyr	Glu	Ile	Pro	Asp	Thr	Gln
		115					120					125			
Met	Ala	Asp	Glu	Lys	Gln	Leu	Glu	Ile	Leu	Gln	Asp	Lys	Ala	Asn	Phe
	130					135					140				
Arg	Ser	Phe	Lys	Pro	Lys	Pro	Phe	Asn	Met	Arg	Glu	Phe	Tyr	Asp	Arg
145					150					155				160	
Ala	Gly	His	Asp	Ile	Arg	Asp	Met	Leu	Leu	Ser	Cys	His	Phe	Arg	Gly
				165				170						175	
Glu	Val	Cys	Ser	Ala	Glu	Asp	Phe	Lys	Val	Val	Phe	Thr	Arg	Tyr	Gly
			180					185					190		
Lys	Cys	Tyr	Thr	Phe	Asn	Ser	Gly	Arg	Asp	Gly	Arg	Pro	Arg	Leu	Lys
		195					200					205			
Thr	Met	Lys	Asp	Gly	Thr	Gly	Asn	Gly	Leu	Glu	Ile	Met	Leu	Asp	Ile
	210					215						220			
Gln	Gln	Asp	Glu	Tyr	Leu	Pro	Val	Trp	Gly	Glu	Thr	Asp	Glu	Thr	Ser
225					230					235				240	
Phe	Glu	Ala	Gly	Ile	Lys	Val	Gln	Ile	His	Ser	Gln	Asp	Glu	Pro	Pro
				245					250					255	
Phe	Ile	Asp	Gln	Leu	Gly	Phe	Gly	Val	Ala	Pro	Gly	Phe	Gln	Thr	Phe
			260					265						270	
Val	Ala	Cys	Gln	Glu	Gln	Arg	Leu	Ile	Tyr	Leu	Pro	Pro	Pro	Trp	Gly
		275					280						285		
Thr	Cys	Lys	Ala	Val	Thr	Met	Asp	Ser	Asp	Leu	Asp	Phe	Phe	Asp	Ser
	290					295					300				
Tyr	Ser	Ile	Thr	Ala	Cys	Arg	Ile	Asp	Cys	Glu	Thr	Arg	Tyr	Leu	Val
305					310					315				320	
Glu	Asn	Cys	Asn	Cys	Arg	Met	Val	His	Met	Pro	Gly	Asp	Ala	Pro	Tyr
				325					330					335	
Cys	Thr	Pro	Glu	Gln	Tyr	Lys	Glu	Cys	Ala	Asp	Pro	Ala	Leu	Asp	Phe
			340						345				350		
Leu	Val	Glu	Lys	Asp	Gln	Glu	Tyr	Cys	Val	Cys	Glu	Met	Pro	Cys	Asn
		355					360					365			
Leu	Thr	Arg	Tyr	Gly	Lys	Glu	Leu	Ser	Met	Val	Lys	Ile	Pro	Ser	Lys
	370					375					380				
Ala	Ser	Ala	Lys	Tyr	Leu	Ala	Lys	Lys	Phe	Asn	Lys	Ser	Glu	Gln	Tyr
385					390					395				400	
Ile	Gly	Glu	Asn	Ile	Leu	Val	Leu	Asp	Ile	Phe	Phe	Glu	Val	Leu	Asn
			405						410					415	
Tyr	Glu	Thr	Ile	Glu	Gln	Lys	Lys	Ala	Tyr	Glu	Ile	Ala	Gly	Leu	Leu
			420					425					430		
Gly	Glu	Leu	Leu	Met	Thr	Pro	Val	Pro	Phe	Ser	Cys	His	Gly	His	Gly
		435					440						445		
Val	Ala	Pro	Tyr	His	Pro	Lys	Ala	Gly	Cys	Ser	Leu	Leu	Ser	His	Glu
	450					455					460				
Gly	Pro	Pro	Pro	Gln	Arg	Pro	Phe	Pro	Lys	Pro	Cys	Cys	Leu	Gly	Asp
465					470					475				480	
Ile	Gly	Gly	Gln	Met	Gly	Leu	Phe	Ile	Gly	Ala	Ser	Ile	Leu	Thr	Val
			485						490					495	
Leu	Glu	Leu	Phe	Asp	Tyr	Ala	Tyr	Glu	Val	Ile	Lys	His	Lys	Leu	Cys
		500						505					510		
Arg	Arg	Gly	Lys	Cys	Gln	Lys	Glu	Ala	Lys	Arg	Ser	Ser	Ala	Asp	Lys
		515					520					525			
Gly	Val	Ala	Leu	Ser	Leu	Asp	Asp	Val	Lys	Arg	His	Asn	Pro	Cys	Glu
	530					535					540				
Ser	Leu	Arg	Gly	His	Pro	Ala	Gly	Met	Thr	Tyr	Ala	Ala	Asn	Ile	Leu

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545          550          555          560
Pro His His Pro Ala Arg Gly Thr Phe Glu Asp Phe Thr Cys
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<212> DNA
<213> Homo sapiens

<220>
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ccc ttg ctg ctg ctg ctg cct ctg ctg aat gtg gag cct gct ggg gcc 102
Pro Leu Leu Leu Leu Leu Pro Leu Leu Asn Val Glu Pro Ala Gly Ala
   10               15               20

aca ctg atc cgg atc cct ctt cgt caa gtc cac cct gga cgc agg acc 150
Thr Leu Ile Arg Ile Pro Leu Arg Gln Val His Pro Gly Arg Arg Thr
   25               30               35               40

ctg aac cta ctg agg gga tgg gga aaa cca gca gag ctc ccc aag ttg 198
Leu Asn Leu Leu Arg Gly Trp Gly Lys Pro Ala Glu Leu Pro Lys Leu
           45               50               55

ggg gcc cca tcc cct ggg gac aag cct gcc tcg gta cct ctc tcc aaa 246
Gly Ala Pro Ser Pro Gly Asp Lys Pro Ala Ser Val Pro Leu Ser Lys
           60               65               70

ttc ctg gat gcc cag tat ttt ggg gaa att ggg ctg gga acg cct cca 294
Phe Leu Asp Ala Gln Tyr Phe Gly Glu Ile Gly Leu Gly Thr Pro Pro
           75               80               85

caa aac ttc act gtt gcc ttt gac act ggc tcc tcc aat ctc tgg gtc 342
Gln Asn Phe Thr Val Ala Phe Asp Thr Gly Ser Ser Asn Leu Trp Val
   90               95               100

ccg tcc agg aga tgc cac ttc ttc agt gtg ccc tgc tgg ttc cac cac 390
Pro Ser Arg Arg Cys His Phe Phe Ser Val Pro Cys Trp Phe His His
  105               110               115               120

cgc ttc aat ccc aat gcc tcc agc tcc ttc aag ccc agt ggg acc aag 438
Arg Phe Asn Pro Asn Ala Ser Ser Ser Phe Lys Pro Ser Gly Thr Lys
           125               130               135

ttt gcc att cag tat gga act ggg cgg gta gat gga atc ctg agt gag 486
Phe Ala Ile Gln Tyr Gly Thr Gly Arg Val Asp Gly Ile Leu Ser Glu
           140               145               150

gac aag ctg act att ggt gga atc aag ggt gca tcc gtg att ttc ggg 534
Asp Lys Leu Thr Ile Gly Gly Ile Lys Gly Ala Ser Val Ile Phe Gly
           155               160               165

gaa gct ctg tgg gaa tcc agc ctg gtc ttc act gtt tcc cgc ccc gat 582
Glu Ala Leu Trp Glu Ser Ser Leu Val Phe Thr Val Ser Arg Pro Asp

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170	175	180	
ggg ata ttg ggc ctc ggt ttt ccc att ctg tct gtg gaa gga gtt cgg Gly Ile Leu Gly Leu Gly Phe Pro Ile Leu Ser Val Glu Gly Val Arg 185 190 195 200			630
ccc ccg ctg gat gta ctg gtg gag cag ggg cta ttg gat aag cct gtc Pro Pro Leu Asp Val Leu Val Glu Gln Gly Leu Leu Asp Lys Pro Val 205 210 215			678
ttc tcc ttt tac ttc aac agg gac cct gaa gtg gct gat gga gga gag Phe Ser Phe Tyr Phe Asn Arg Asp Pro Glu Val Ala Asp Gly Gly Glu 220 225 230			726
ctg gtc ctg ggg ggc tca gac ccg gca cac tac atc cca ccc ctc acc Leu Val Leu Gly Gly Ser Asp Pro Ala His Tyr Ile Pro Pro Leu Thr 235 240 245			774
ttc gtg cca gtc aca gtc ccc gcc tac tgg cag atc cac atg gag cgt Phe Val Pro Val Thr Val Pro Ala Tyr Trp Gln Ile His Met Glu Arg 250 255 260			822
gtg aag gtg ggc tca cgg ctg act ctc tgt gcc cag ggc tgt gct gcc Val Lys Val Gly Ser Arg Leu Thr Leu Cys Ala Gln Gly Cys Ala Ala 265 270 275 280			870
atc ctg gat aca ggc aca cct gtc atc gta gga ccc act gag gag atc Ile Leu Asp Thr Gly Thr Pro Val Ile Val Gly Pro Thr Glu Glu Ile 285 290 295			918
cgg gcc ctg cat gca gcc att ggg gga atc ccc ttg ctg gct ggg gag Arg Ala Leu His Ala Ala Ile Gly Gly Ile Pro Leu Leu Ala Gly Glu 300 305 310			966
tac atc atc cgg tgc tca gaa atc cca aag ctc ccc gca gtc tca ctc Tyr Ile Ile Arg Cys Ser Glu Ile Pro Lys Leu Pro Ala Val Ser Leu 315 320 325			1014
ctc att ggg ggg gtc tgg ttt aat ctc acg gcc cag gat tac gtc atc Leu Ile Gly Gly Val Trp Phe Asn Leu Thr Ala Gln Asp Tyr Val Ile 330 335 340			1062
cag ttt gct cag ggt gac gtc cgc ctc tgc ttg tcc ggc ttc cgg gcc Gln Phe Ala Gln Gly Asp Val Arg Leu Cys Leu Ser Gly Phe Arg Ala 345 350 355 360			1110
ttg gac atc gct tgc cct cca gta cct gtg tgg atc ctc ggc gac gtt Leu Asp Ile Ala Ser Pro Pro Val Pro Val Trp Ile Leu Gly Asp Val 365 370 375			1158
ttc ttg ggg gcg tat gtg acc gtc ttc gac cgc ggg gac atg aag agc Phe Leu Gly Ala Tyr Val Thr Val Phe Asp Arg Gly Asp Met Lys Ser 380 385 390			1206
ggc gca cga gtg gga ctg gcg cgc gct cgc cct cgc gga gcg gac ctg Gly Ala Arg Val Gly Leu Ala Arg Ala Arg Pro Arg Gly Ala Asp Leu 395 400 405			1254
gga agg cgc gag acc gcg cag gcg cag tac cgc ggg tgc cgc cca ggt Gly Arg Arg Glu Thr Ala Gln Ala Gln Tyr Arg Gly Cys Arg Pro Gly 410 415 420			1302

gat gcg cat gcg cac cgg gta gca gag cta gcg cta ctc agt aaa aat 1350  
 Asp Ala His Ala His Arg Val Ala Glu Leu Ala Leu Leu Ser Lys Asn  
 425 430 435 440

cca ata ttt cca ttg aaa aaa aa 1373  
 Pro Ile Phe Pro Leu Lys Lys  
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 20 25 30  
 Gln Val His Pro Gly Arg Arg Thr Leu Asn Leu Leu Arg Gly Trp Gly  
 35 40 45  
 Lys Pro Ala Glu Leu Pro Lys Leu Gly Ala Pro Ser Pro Gly Asp Lys  
 50 55 60  
 Pro Ala Ser Val Pro Leu Ser Lys Phe Leu Asp Ala Gln Tyr Phe Gly  
 65 70 75 80  
 Glu Ile Gly Leu Gly Thr Pro Pro Gln Asn Phe Thr Val Ala Phe Asp  
 85 90 95  
 Thr Gly Ser Ser Asn Leu Trp Val Pro Ser Arg Arg Cys His Phe Phe  
 100 105 110  
 Ser Val Pro Cys Trp Phe His His Arg Phe Asn Pro Asn Ala Ser Ser  
 115 120 125  
 Ser Phe Lys Pro Ser Gly Thr Lys Phe Ala Ile Gln Tyr Gly Thr Gly  
 130 135 140  
 Arg Val Asp Gly Ile Leu Ser Glu Asp Lys Leu Thr Ile Gly Gly Ile  
 145 150 155 160  
 Lys Gly Ala Ser Val Ile Phe Gly Glu Ala Leu Trp Glu Ser Ser Leu  
 165 170 175  
 Val Phe Thr Val Ser Arg Pro Asp Gly Ile Leu Gly Leu Gly Phe Pro  
 180 185 190  
 Ile Leu Ser Val Glu Gly Val Arg Pro Pro Leu Asp Val Leu Val Glu  
 195 200 205  
 Gln Gly Leu Leu Asp Lys Pro Val Phe Ser Phe Tyr Phe Asn Arg Asp  
 210 215 220  
 Pro Glu Val Ala Asp Gly Gly Glu Leu Val Leu Gly Gly Ser Asp Pro  
 225 230 235 240  
 Ala His Tyr Ile Pro Pro Leu Thr Phe Val Pro Val Thr Val Pro Ala  
 245 250 255  
 Tyr Trp Gln Ile His Met Glu Arg Val Lys Val Gly Ser Arg Leu Thr  
 260 265 270  
 Leu Cys Ala Gln Gly Cys Ala Ala Ile Leu Asp Thr Gly Thr Pro Val  
 275 280 285  
 Ile Val Gly Pro Thr Glu Glu Ile Arg Ala Leu His Ala Ala Ile Gly  
 290 295 300  
 Gly Ile Pro Leu Leu Ala Gly Glu Tyr Ile Ile Arg Cys Ser Glu Ile  
 305 310 315 320

Pro Lys Leu Pro Ala Val Ser Leu Leu Ile Gly Gly Val Trp Phe Asn  
 325 330 335  
 Leu Thr Ala Gln Asp Tyr Val Ile Gln Phe Ala Gln Gly Asp Val Arg  
 340 345 350  
 Leu Cys Leu Ser Gly Phe Arg Ala Leu Asp Ile Ala Ser Pro Pro Val  
 355 360 365  
 Pro Val Trp Ile Leu Gly Asp Val Phe Leu Gly Ala Tyr Val Thr Val  
 370 375 380  
 Phe Asp Arg Gly Asp Met Lys Ser Gly Ala Arg Val Gly Leu Ala Arg  
 385 390 395 400  
 Ala Arg Pro Arg Gly Ala Asp Leu Gly Arg Arg Glu Thr Ala Gln Ala  
 405 410 415  
 Gln Tyr Arg Gly Cys Arg Pro Gly Asp Ala His Ala His Arg Val Ala  
 420 425 430  
 Glu Leu Ala Leu Leu Ser Lys Asn Pro Ile Phe Pro Leu Lys Lys Xaa  
 435 440 445

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 aag att caa tat act aag atc ttc ata aac aat gaa tgg cat gat tca 96  
 Lys Ile Gln Tyr Thr Lys Ile Phe Ile Asn Asn Glu Trp His Asp Ser  
 20 25 30  
 gtg agt ggc aag aaa ttt cct gtc ttt aat cct gca act gag gag gag 144  
 Val Ser Gly Lys Lys Phe Pro Val Phe Asn Pro Ala Thr Glu Glu Glu  
 35 40 45  
 ctc tgc cag gta gaa gaa gga gat aag gag gat gtt gac aag gca gtg 192  
 Leu Cys Gln Val Glu Glu Gly Asp Lys Glu Asp Val Asp Lys Ala Val  
 50 55 60  
 aag gcc gca aga cag gct ttt cag att gga tct ccg tgg cgt act atg 240  
 Lys Ala Ala Arg Gln Ala Phe Gln Ile Gly Ser Pro Trp Arg Thr Met  
 65 70 75 80  
 gat gct tcc gag agg ggg cga cta tta tac aag ttg gct gat tta atc 288  
 Asp Ala Ser Glu Arg Gly Arg Leu Leu Tyr Lys Leu Ala Asp Leu Ile  
 85 90 95  
 gaa aga gat cgt ctg ctg ctg gcg aca atg gag tca atg aat ggt gga 336  
 Glu Arg Asp Arg Leu Leu Leu Ala Thr Met Glu Ser Met Asn Gly Gly  
 100 105 110  
 aaa ctc tat tcc aat gca tat ctg agt gat tta gca ggc tgc atc aaa 384  
 Lys Leu Tyr Ser Asn Ala Tyr Leu Ser Asp Leu Ala Gly Cys Ile Lys  
 115 120 125

aca ttg cgc tac tgt gca ggt tgg gct gac aag atc cag ggc cgt aca Thr Leu Arg Tyr Cys Ala Gly Trp Ala Asp Lys Ile Gln Gly Arg Thr 130 135 140	432
ata cca att gat gga aat ttt ttt aca tat aca aga cat gaa cct att Ile Pro Ile Asp Gly Asn Phe Phe Thr Tyr Thr Arg His Glu Pro Ile 145 150 155 160	480
ggt gta tgt ggc caa atc att cct tgg aat ttc ccg ttg gtt atg ctc Gly Val Cys Gly Gln Ile Ile Pro Trp Asn Phe Pro Leu Val Met Leu 165 170 175	528
att tgg aag ata ggg cct gca ctg agc tgt gga aac aca gtg gtt gtc Ile Trp Lys Ile Gly Pro Ala Leu Ser Cys Gly Asn Thr Val Val Val 180 185 190	576
aaa cca gca gag caa act cct ctc act gct ctc cac gtg gca tct tta Lys Pro Ala Glu Gln Thr Pro Leu Thr Ala Leu His Val Ala Ser Leu 195 200 205	624
ata aaa gag gca ggg ttt cct cct gga gta gtg aat att gtt cct ggt Ile Lys Glu Ala Gly Phe Pro Pro Gly Val Val Asn Ile Val Pro Gly 210 215 220	672
tat ggg cct aca gca ggg gca gcc att tct tct cac atg gat ata gac Tyr Gly Pro Thr Ala Gly Ala Ala Ile Ser Ser His Met Asp Ile Asp 225 230 235 240	720
aaa gta gcc ttc aca gga tca aca gag gtt ggc aag ttg atc aaa gaa Lys Val Ala Phe Thr Gly Ser Thr Glu Val Gly Lys Leu Ile Lys Glu 245 250 255	768
gct gcc ggg aaa agc aat ctg aag agg gtg acc ctg gag ctt gga gga Ala Ala Gly Lys Ser Asn Leu Lys Arg Val Thr Leu Glu Leu Gly Gly 260 265 270	816
aag agc cct tgc att gtg tta gct gat gcc gac ttg gac aat gct gtt Lys Ser Pro Cys Ile Val Leu Ala Asp Ala Asp Leu Asp Asn Ala Val 275 280 285	864
gaa ttt gca cac cat ggg gta ttc tac cac cag ggc cag tgt tgt ata Glu Phe Ala His His Gly Val Phe Tyr His Gln Gly Gln Cys Cys Ile 290 295 300	912
gcc gca tcc agg att ttt gtg gaa gaa tca att tat gat gag ttt gtt Ala Ala Ser Arg Ile Phe Val Glu Glu Ser Ile Tyr Asp Glu Phe Val 305 310 315 320	960
cga agg agt gtt gag cgg gct aag aag tat atc ctt gga aat cct ctg Arg Arg Ser Val Glu Arg Ala Lys Lys Tyr Ile Leu Gly Asn Pro Leu 325 330 335	1008
acc cca gga gtc act caa ggc cct cag att gac aag gaa caa tat gat Thr Pro Gly Val Thr Gln Gly Pro Gln Ile Asp Lys Glu Gln Tyr Asp 340 345 350	1056
aaa ata ctt gac ctc att gag agt ggg aag aaa gaa ggg gcc aaa ctg Lys Ile Leu Asp Leu Ile Glu Ser Gly Lys Lys Glu Gly Ala Lys Leu 355 360 365	1104
gaa tgt gga gga ggc ccg tgg ggg aat aaa ggc tac ttt gtc cag ccc	1152



Glu Cys Gly Gly Gly Pro Trp Gly Asn Lys Gly Tyr Phe Val Gln Pro  
 370 375 380  
 aca gtg ttc tct aat gtt aca gat gag atg cgc att gcc aaa gag gag 1200  
 Thr Val Phe Ser Asn Val Thr Asp Glu Met Arg Ile Ala Lys Glu Glu  
 385 390 395 400  
 att ttt gga cca gtg cag caa atc atg aag ttt aaa tct tta gat gac 1248  
 Ile Phe Gly Pro Val Gln Gln Ile Met Lys Phe Lys Ser Leu Asp Asp  
 405 410 415  
 gtg atc aaa aga gca aac aat act ttc tat ggc tta tca gca gga gtg 1296  
 Val Ile Lys Arg Ala Asn Asn Thr Phe Tyr Gly Leu Ser Ala Gly Val  
 420 425 430  
 ttt acc aaa gac att gat aaa gcc ata aca atc tcc tct gct ctg cag 1344  
 Phe Thr Lys Asp Ile Asp Lys Ala Ile Thr Ile Ser Ser Ala Leu Gln  
 435 440 445  
 gca gga aca gtg tgg gtg aat tgc tat ggc gtg gta agt gcc cag tgc 1392  
 Ala Gly Thr Val Trp Val Asn Cys Tyr Gly Val Val Ser Ala Gln Cys  
 450 455 460  
 ccc ttt ggc gga ttc aag atg tct gga aat gga aga gaa ctg gga gag 1440  
 Pro Phe Gly Gly Phe Lys Met Ser Gly Asn Gly Arg Glu Leu Gly Glu  
 465 470 475 480  
 tac ggt ttc cat gaa tat aca gag gtc aaa aca gtc aca gtg aaa atc 1488  
 Tyr Gly Phe His Glu Tyr Thr Glu Val Lys Thr Val Thr Val Lys Ile  
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 tct cag aag aac tca taa 1506  
 Ser Gln Lys Asn Ser \*  
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 <211> 501  
 <212> PRT  
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 Val Ser Gly Lys Lys Phe Pro Val Phe Asn Pro Ala Thr Glu Glu Glu  
 35 40 45  
 Leu Cys Gln Val Glu Glu Gly Asp Lys Glu Asp Val Asp Lys Ala Val  
 50 55 60  
 Lys Ala Ala Arg Gln Ala Phe Gln Ile Gly Ser Pro Trp Arg Thr Met  
 65 70 75 80  
 Asp Ala Ser Glu Arg Gly Arg Leu Leu Tyr Lys Leu Ala Asp Leu Ile  
 85 90 95  
 Glu Arg Asp Arg Leu Leu Leu Ala Thr Met Glu Ser Met Asn Gly Gly  
 100 105 110  
 Lys Leu Tyr Ser Asn Ala Tyr Leu Ser Asp Leu Ala Gly Cys Ile Lys  
 115 120 125  
 Thr Leu Arg Tyr Cys Ala Gly Trp Ala Asp Lys Ile Gln Gly Arg Thr  
 130 135 140  
 Ile Pro Ile Asp Gly Asn Phe Phe Thr Tyr Thr Arg His Glu Pro Ile

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<210> 23
<211> 3257
<212> DNA
<213> Homo sapiens
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gccccgcgcc cgacc atg gcc gag gag ctg gtc tta.gag agg tgt gat ctg 171
Met Ala Glu Glu Leu Val Leu Glu Arg Cys Asp Leu
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	1	5	10	
	gag ctg gag acc aat ggc cga gac cac cac acg gcc gac ctg tgc cgg	219		
	Glu Leu Glu Thr Asn Gly Arg Asp His His Thr Ala Asp Leu Cys Arg			
	15 20 25			
	gag aag ctg gtg gtg cga cgg ggc cag ccc ttc tgg ctg acc ctg cac	267		
	Glu Lys Leu Val Val Arg Arg Gly Gln Pro Phe Trp Leu Thr Leu His			
	30 35 40			
	ttt gag ggc cgc aac tac cag gcc agt gta gac agt ctc acc ttc agt	315		
	Phe Glu Gly Arg Asn Tyr Gln Ala Ser Val Asp Ser Leu Thr Phe Ser			
	45 50 55 60			
	gtc gtg acc ggc cca gcc cct agc cag gag gcc ggg acc aag gcc cgt	363		
	Val Val Thr Gly Pro Ala Pro Ser Gln Glu Ala Gly Thr Lys Ala Arg			
	65 70 75			
	ttt cca cta aga gat gct gtg gag gag ggt gac tgg aca gcc acc gtg	411		
	Phe Pro Leu Arg Asp Ala Val Glu Glu Gly Asp Trp Thr Ala Thr Val			
	80 85 90			
	gtg gac cag caa gac tgc acc ctc tcg ctg cag ctc acc acc ccg gcc	459		
	Val Asp Gln Gln Asp Cys Thr Leu Ser Leu Gln Leu Thr Thr Pro Ala			
	95 100 105			
	aac gcc ccc atc ggc ctg tat cgc ctc agc ctg gag gcc tcc act ggc	507		
	Asn Ala Pro Ile Gly Leu Tyr Arg Leu Ser Leu Glu Ala Ser Thr Gly			
	110 115 120			
	tac cag gga tcc agc ttt gtg ctg ggc cac ttc att ttg ctc ttc aac	555		
	Tyr Gln Gly Ser Ser Phe Val Leu Gly His Phe Ile Leu Leu Phe Asn			
	125 130 135 140			
	gcc tgg tgc cca gcg gat gct gtg tac ctg gac tcg gaa gag gag cgg	603		
	Ala Trp Cys Pro Ala Asp Ala Val Tyr Leu Asp Ser Glu Glu Glu Arg			
	145 150 155			
	cag gag tat gtc ctc acc cag cag ggc ttt atc tac cag ggc tcg gcc	651		
	Gln Glu Tyr Val Leu Thr Gln Gln Gly Phe Ile Tyr Gln Gly Ser Ala			
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	aag ttc atc aag aac ata cct tgg aat ttt ggg cag ttt caa gat ggg	699		
	Lys Phe Ile Lys Asn Ile Pro Trp Asn Phe Gly Gln Phe Gln Asp Gly			
	175 180 185			
	atc cta gac atc tgc ctg atc ctt cta gat gtc aac ccc aag ttc ctg	747		
	Ile Leu Asp Ile Cys Leu Ile Leu Leu Asp Val Asn Pro Lys Phe Leu			
	190 195 200			
	aag aac gcc ggc cgt gac tgc tcc cgg cgc agc agc ccc gtc tac gtg	795		
	Lys Asn Ala Gly Arg Asp Cys Ser Arg Arg Ser Ser Pro Val Tyr Val			
	205 210 215 220			
	ggc cgg gtg ggt agt ggc atg gtc aac tgc aac gat gac cag ggt gtg	843		
	Gly Arg Val Gly Ser Gly Met Val Asn Cys Asn Asp Asp Gln Gly Val			
	225 230 235			
	ctg ctg gga cgc tgg gac aac aac tac ggg gac ggc gtc agc ccc atg	891		
	Leu Leu Gly Arg Trp Asp Asn Asn Tyr Gly Asp Gly Val Ser Pro Met			
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 Ser Trp Ile Gly Ser Val Asp Ile Leu Arg Arg Trp Lys Asn His Gly  
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tgc cag cgc gtc aag tat ggc cag tgc tgg gtc ttc gcc gcc gtg gcc 987  
 Cys Gln Arg Val Lys Tyr Gly Gln Cys Trp Val Phe Ala Ala Val Ala  
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tgc aca gtg ctg agg tgc cta ggc atc cct acc cgc gtc gtg acc aac 1035  
 Cys Thr Val Leu Arg Cys Leu Gly Ile Pro Thr Arg Val Val Thr Asn  
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 Tyr Asn Ser Ala His Asp Gln Asn Ser Asn Leu Leu Ile Glu Tyr Phe  
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cgc aat gag ttt ggg gag atc cag ggt gac aag agc gag atg atc tgg 1131  
 Arg Asn Glu Phe Gly Glu Ile Gln Gly Asp Lys Ser Glu Met Ile Trp  
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 Asn Phe His Cys Trp Val Glu Ser Trp Met Thr Arg Pro Asp Leu Gln  
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ccg ggg tac gag ggc tgg cag gcc ctg gac cca acg ccc cag gag aag 1227  
 Pro Gly Tyr Glu Gly Trp Gln Ala Leu Asp Pro Thr Pro Gln Glu Lys  
 350 355 360

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 Ser Glu Gly Thr Tyr Cys Cys Gly Pro Val Pro Val Arg Ala Ile Lys  
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gag ggc gac ctg agc acc aag tac gat gcg ccc ttt gtc ttt gcg gag 1323  
 Glu Gly Asp Leu Ser Thr Lys Tyr Asp Ala Pro Phe Val Phe Ala Glu  
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 His Lys Ser Ile Asn Arg Ser Leu Ile Val Gly Leu Lys Ile Ser Thr  
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aag agc gtg ggc cga gac gag cgg gag gat atc acc cac acc tac aaa 1467  
 Lys Ser Val Gly Arg Asp Glu Arg Glu Asp Ile Thr His Thr Tyr Lys  
 430 435 440

tac cca gag ggg tcc tca gag gag agg gag gcc ttc aca agg gcg aac 1515  
 Tyr Pro Glu Gly Ser Ser Glu Glu Arg Glu Ala Phe Thr Arg Ala Asn  
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 His Leu Asn Lys Leu Ala Glu Lys Glu Glu Thr Gly Met Ala Met Arg  
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atc cgt gtg ggc cag agc atg aac atg ggc agt gac ttt gac gtc ttt 1611  
 Ile Arg Val Gly Gln Ser Met Asn Met Gly Ser Asp Phe Asp Val Phe  
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gcc cac atc acc aac aac acc gct gag gag tac gtc tgc cgc ctc ctg 1659  
 Ala His Ile Thr Asn Asn Thr Ala Glu Glu Tyr Val Cys Arg Leu Leu  
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ggc acc aag tac ctg ctc aac cta acc ctg gag cct ttc tct gag aag 1755  
 Gly Thr Lys Tyr Leu Leu Asn Leu Thr Leu Glu Pro Phe Ser Glu Lys  
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 Ser Val Pro Leu Cys Ile Leu Tyr Glu Lys Tyr Arg Asp Cys Leu Thr  
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aac agc tac ctg ctg gct gag agg gac ctc tac ctg gag aat cca gaa 1899  
 Asn Ser Tyr Leu Leu Ala Glu Arg Asp Leu Tyr Leu Glu Asn Pro Glu  
 575 580 585

atc aag atc cgg atc ctt ggg gag ccc aag cag aaa cgc aag ctg gtg 1947  
 Ile Lys Ile Arg Ile Leu Gly Glu Pro Lys Gln Lys Arg Lys Leu Val  
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gct gag gtg tcc ctg cag aac ccg ctc cct gtg gcc ctg gaa ggc tgc 1995  
 Ala Glu Val Ser Leu Gln Asn Pro Leu Pro Val Ala Leu Glu Gly Cys  
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acc ttc act gtg gag ggg gcc ggc ctg act gag gag cag aag acg gtg 2043  
 Thr Phe Thr Val Glu Gly Ala Gly Leu Thr Glu Glu Gln Lys Thr Val  
 625 630 635

gag atc cca gac ccc gtg gag gca ggg gag gaa gtt aag gtg aga atg 2091  
 Glu Ile Pro Asp Pro Val Glu Ala Gly Glu Glu Val Lys Val Arg Met  
 640 645 650

gac ctc gtg ccg ctc cac atg ggc ctc cac aag ctg gtg gtg aac ttc 2139  
 Asp Leu Val Pro Leu His Met Gly Leu His Lys Leu Val Val Asn Phe  
 655 660 665

gag agc gac aag ctg aag gct gtg aag ggc ttc cgg aat gtc atc att 2187  
 Glu Ser Asp Lys Leu Lys Ala Val Lys Gly Phe Arg Asn Val Ile Ile  
 670 675 680

ggc ccc gcc taa gggaccctg ctcccagcct gctgagagcc cccacctga 2239  
 Gly Pro Ala \*  
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 cccttgggac acccagagct ggggtggggac agtgataggc ccaagggtccc ctccacatcc 2719  
 cagcagccca agcttaatag ccctccccct caacctcacc attgtgaagc acctactatg 2779

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tctggccagc gactgccttc tcctctctgg gcctttgttt ccttggtggt cagaggagtg 3199
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<211> 687

<212> PRT

<213> Homo sapiens

<400> 24

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Val Arg Arg Gly Gln Pro Phe Trp Leu Thr Leu His Phe Glu Gly Arg
  35          40          45
Asn Tyr Gln Ala Ser Val Asp Ser Leu Thr Phe Ser Val Val Thr Gly
  50          55          60
Pro Ala Pro Ser Gln Glu Ala Gly Thr Lys Ala Arg Phe Pro Leu Arg
  65          70          75          80
Asp Ala Val Glu Glu Gly Asp Trp Thr Ala Thr Val Val Asp Gln Gln
  85          90          95
Asp Cys Thr Leu Ser Leu Gln Leu Thr Thr Pro Ala Asn Ala Pro Ile
  100          105          110
Gly Leu Tyr Arg Leu Ser Leu Glu Ala Ser Thr Gly Tyr Gln Gly Ser
  115          120          125
Ser Phe Val Leu Gly His Phe Ile Leu Leu Phe Asn Ala Trp Cys Pro
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Ala Asp Ala Val Tyr Leu Asp Ser Glu Glu Glu Arg Gln Glu Tyr Val
  145          150          155          160
Leu Thr Gln Gln Gly Phe Ile Tyr Gln Gly Ser Ala Lys Phe Ile Lys
  165          170          175
Asn Ile Pro Trp Asn Phe Gly Gln Phe Gln Asp Gly Ile Leu Asp Ile
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Cys Leu Ile Leu Leu Asp Val Asn Pro Lys Phe Leu Lys Asn Ala Gly
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Arg Asp Cys Ser Arg Arg Ser Ser Pro Val Tyr Val Gly Arg Val Gly
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Ser Gly Met Val Asn Cys Asn Asp Asp Gln Gly Val Leu Leu Gly Arg
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Trp Asp Asn Asn Tyr Gly Asp Gly Val Ser Pro Met Ser Trp Ile Gly
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Ser Val Asp Ile Leu Arg Arg Trp Lys Asn His Gly Cys Gln Arg Val
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Lys Tyr Gly Gln Cys Trp Val Phe Ala Ala Val Ala Cys Thr Val Leu
  275          280          285
Arg Cys Leu Gly Ile Pro Thr Arg Val Val Thr Asn Tyr Asn Ser Ala
  290          295          300
His Asp Gln Asn Ser Asn Leu Leu Ile Glu Tyr Phe Arg Asn Glu Phe
  305          310          315          320
Gly Glu Ile Gln Gly Asp Lys Ser Glu Met Ile Trp Asn Phe His Cys
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Trp Val Glu Ser Trp Met Thr Arg Pro Asp Leu Gln Pro Gly Tyr Glu
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Gly Trp Gln Ala Leu Asp Pro Thr Pro Gln Glu Lys Ser Glu Gly Thr

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Tyr Cys Cys Gly Pro Val Pro Val Arg Ala Ile Lys Glu Gly Asp Leu
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Ser Thr Lys Tyr Asp Ala Pro Phe Val Phe Ala Glu Val Asn Ala Asp
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Val Val Asp Trp Ile Gln Gln Asp Asp Gly Ser Val His Lys Ser Ile
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Asn Arg Ser Leu Ile Val Gly Leu Lys Ile Ser Thr Lys Ser Val Gly
      420              425              430
Arg Asp Glu Arg Glu Asp Ile Thr His Thr Tyr Lys Tyr Pro Glu Gly
      435              440              445
Ser Ser Glu Glu Arg Glu Ala Phe Thr Arg Ala Asn His Leu Asn Lys
      450              455              460
Leu Ala Glu Lys Glu Glu Thr Gly Met Ala Met Arg Ile Arg Val Gly
      465              470              475              480
Gln Ser Met Asn Met Gly Ser Asp Phe Asp Val Phe Ala His Ile Thr
      485              490              495
Asn Asn Thr Ala Glu Glu Tyr Val Cys Arg Leu Leu Leu Cys Ala Arg
      500              505              510
Thr Val Ser Tyr Asn Gly Ile Leu Gly Pro Glu Cys Gly Thr Lys Tyr
      515              520              525
Leu Leu Asn Leu Thr Leu Glu Pro Phe Ser Glu Lys Ser Val Pro Leu
      530              535              540
Cys Ile Leu Tyr Glu Lys Tyr Arg Asp Cys Leu Thr Glu Ser Asn Leu
      545              550              555              560
Ile Lys Val Arg Ala Leu Leu Val Glu Pro Val Ile Asn Ser Tyr Leu
      565              570              575
Leu Ala Glu Arg Asp Leu Tyr Leu Glu Asn Pro Glu Ile Lys Ile Arg
      580              585              590
Ile Leu Gly Glu Pro Lys Gln Lys Arg Lys Leu Val Ala Glu Val Ser
      595              600              605
Leu Gln Asn Pro Leu Pro Val Ala Leu Glu Gly Cys Thr Phe Thr Val
      610              615              620
Glu Gly Ala Gly Leu Thr Glu Glu Gln Lys Thr Val Glu Ile Pro Asp
      625              630              635              640
Pro Val Glu Ala Gly Glu Glu Val Lys Val Arg Met Asp Leu Val Pro
      645              650              655
Leu His Met Gly Leu His Lys Leu Val Val Asn Phe Glu Ser Asp Lys
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Leu Lys Ala Val Lys Gly Phe Arg Asn Val Ile Ile Gly Pro Ala
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&lt;210&gt; 25

&lt;211&gt; 1061

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (11)...(1051)

&lt;400&gt; 25

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5

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His Trp Phe Val Phe Ser Val Tyr Leu Leu Thr Phe Leu Val Gly Leu

15

20

25

ccc ctc aac ctg ctg gcc ctg gtg gtc ttc gtg ggc aag ctg cag cgc 145  
Pro Leu Asn Leu Leu Ala Leu Val Val Phe Val Gly Lys Leu Gln Arg  
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cgc ccg gtg gcc gtg gac gtg ctc ctg ctc aac ctg acc gcc tcg gac 193  
Arg Pro Val Ala Val Asp Val Leu Leu Leu Asn Leu Thr Ala Ser Asp  
50 55 60  
  
ctg ctc ctg ctg ctg ttc ctg cct ttc cgc atg gtg gag gca gcc aat 241  
Leu Leu Leu Leu Leu Phe Leu Pro Phe Arg Met Val Glu Ala Ala Asn  
65 70 75  
  
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Gly Met His Trp Pro Leu Pro Phe Ile Leu Cys Pro Leu Ser Gly Phe  
80 85 90  
  
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Ile Phe Phe Thr Thr Ile Tyr Leu Thr Ala Leu Phe Leu Ala Ala Val  
95 100 105  
  
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Ser Ile Glu Arg Phe Leu Ser Val Ala His Pro Leu Trp Tyr Lys Thr  
110 115 120 125  
  
cgg ccg agg ctg ggg cag gca ggt ctg gtg agt gtg gcc tgc tgg ctg 433  
Arg Pro Arg Leu Gly Gln Ala Gly Leu Val Ser Val Ala Cys Trp Leu  
130 135 140  
  
ttg gcc tct gct cac tgc agc gtg gtc tac gtc ata gaa ttc tca ggg 481  
Leu Ala Ser Ala His Cys Ser Val Val Tyr Val Ile Glu Phe Ser Gly  
145 150 155  
  
gac atc tcc cac agc cag ggc acc aat ggg acc tgc tac ctg gag ttc 529  
Asp Ile Ser His Ser Gln Gly Thr Asn Gly Thr Cys Tyr Leu Glu Phe  
160 165 170  
  
cgg aag gac cag cta gcc atc ctc ctg ccc gtg cgg ctg gag atg gct 577  
Arg Lys Asp Gln Leu Ala Ile Leu Leu Pro Val Arg Leu Glu Met Ala  
175 180 185  
  
gtg gtc ctc ttt gtg gtc ccg ctg atc atc acc agc tac tgc tac agc 625  
Val Val Leu Phe Val Val Pro Leu Ile Ile Thr Ser Tyr Cys Tyr Ser  
190 195 200 205  
  
cgc ctg gtg tgg atc ctc ggc aga ggg ggc agc cac cgc cgg cag agg 673  
Arg Leu Val Trp Ile Leu Gly Arg Gly Gly Ser His Arg Arg Gln Arg  
210 215 220  
  
agg gtg gcg ggg ctg ttg gcg gcc acg ctg ctc aac ttc ctt gtc tgc 721  
Arg Val Ala Gly Leu Leu Ala Ala Thr Leu Leu Asn Phe Leu Val Cys  
225 230 235  
  
ttt ggg ccc tac aac gtg tcc cat gtc gtg ggc tat atc tgc ggt gaa 769  
Phe Gly Pro Tyr Asn Val Ser His Val Val Gly Tyr Ile Cys Gly Glu  
240 245 250  
  
agc ccg gca tgg agg atc tac gtg acg ctt ctc agc acc ctg aac tcc 817  
Ser Pro Ala Trp Arg Ile Tyr Val Thr Leu Leu Ser Thr Leu Asn Ser  
255 260 265  
  
tgt gtc gac ccc ttt gtc tac tac ttc tcc tcc tcc ggg ttc caa gcc 865



Cys Val Asp Pro Phe Val Tyr Tyr Phe Ser Ser Ser Gly Phe Gln Ala  
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 Asp Phe His Glu Leu Leu Arg Arg Leu Cys Gly Leu Trp Gly Gln Trp  
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 Gln Gln Glu Ser Ser Met Glu Leu Lys Glu Gln Lys Gly Gly Glu Glu  
 305 310 315  
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 Gln Arg Ala Asp Arg Pro Ala Glu Arg Lys Thr Ser Glu His Ser Gln  
 320 325 330  
 ggc tgt gga act ggt ggc cag gtg gcc tgt gct gaa agc tag 1051  
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 Ala Val Asp Val Leu Leu Leu Asn Leu Thr Ala Ser Asp Leu Leu Leu  
 50 55 60  
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 65 70 75 80  
 Trp Pro Leu Pro Phe Ile Leu Cys Pro Leu Ser Gly Phe Ile Phe Phe  
 85 90 95  
 Thr Thr Ile Tyr Leu Thr Ala Leu Phe Leu Ala Ala Val Ser Ile Glu  
 100 105 110  
 Arg Phe Leu Ser Val Ala His Pro Leu Trp Tyr Lys Thr Arg Pro Arg  
 115 120 125  
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 His Ser Gln Gly Thr Asn Gly Thr Cys Tyr Leu Glu Phe Arg Lys Asp  
 165 170 175  
 Gln Leu Ala Ile Leu Leu Pro Val Arg Leu Glu Met Ala Val Val Leu  
 180 185 190  
 Phe Val Val Pro Leu Ile Ile Thr Ser Tyr Cys Tyr Ser Arg Leu Val  
 195 200 205  
 Trp Ile Leu Gly Arg Gly Gly Ser His Arg Arg Gln Arg Arg Val Ala  
 210 215 220  
 Gly Leu Leu Ala Ala Thr Leu Leu Asn Phe Leu Val Cys Phe Gly Pro  
 225 230 235 240  
 Tyr Asn Val Ser His Val Val Gly Tyr Ile Cys Gly Glu Ser Pro Ala  
 245 250 255  
 Trp Arg Ile Tyr Val Thr Leu Leu Ser Thr Leu Asn Ser Cys Val Asp  
 260 265 270

Pro Phe Val Tyr Tyr Phe Ser Ser Ser Gly Phe Gln Ala Asp Phe His  
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 Glu Leu Leu Arg Arg Leu Cys Gly Leu Trp Gly Gln Trp Gln Gln Glu  
                   290                  295                  300  
 Ser Ser Met Glu Leu Lys Glu Gln Lys Gly Gly Glu Glu Gln Arg Ala  
 305                  310                  315                  320  
 Asp Arg Pro Ala Glu Arg Lys Thr Ser Glu His Ser Gln Gly Cys Gly  
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                   15                  20                  25  
  
 cgg gcc ttt gtg ggg cgg atc cgc cag ccc cag cct gca cct gtg cac 145  
 Arg Ala Phe Val Gly Arg Ile Arg Gln Pro Gln Pro Ala Pro Val His  
                   30                  35                  40                  45  
  
 atc ctc ctg ctg agc ctg acg ctg gcc gac ctc ctc ctg ctg ctg ctg 193  
 Ile Leu Leu Leu Ser Leu Thr Leu Ala Asp Leu Leu Leu Leu Leu Leu  
                   50                  55                  60  
  
 ctg ccc ttc aag atc atc gag gct gcg tgc aac ttc cgc tgg tac ctg 241  
 Leu Pro Phe Lys Ile Ile Glu Ala Ala Ser Asn Phe Arg Trp Tyr Leu  
                   65                  70                  75  
  
 ccc aag gtc gtc tgc gcc ctc acg agt ttt ggc ttc tac agc agc atc 289  
 Pro Lys Val Val Cys Ala Leu Thr Ser Phe Gly Phe Tyr Ser Ser Ile  
                   80                  85                  90  
  
 tac tgc agc acg tgg ctc ctg gcg ggc atc agc atc gag cgc tac ctg 337  
 Tyr Cys Ser Thr Trp Leu Leu Ala Gly Ile Ser Ile Glu Arg Tyr Leu  
                   95                  100                  105  
  
 gga gtg gct ttc ccc gtg cag tac aag ctc tcc cgc cgg cct ctg tat 385  
 Gly Val Ala Phe Pro Val Gln Tyr Lys Leu Ser Arg Arg Pro Leu Tyr  
                   110                  115                  120                  125  
  
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 Gly Val Ile Ala Ala Leu Val Ala Trp Val Met Ser Phe Gly His Cys  
                   130                  135                  140  
  
 acc atc gtg atc atc gtt caa tac ttg aac acg act gag cag gtc aga 481  
 Thr Ile Val Ile Ile Val Gln Tyr Leu Asn Thr Thr Glu Gln Val Arg  
                   145                  150                  155

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gac gtg gtg ctg ccc gtg cgg ctg gag ctg tgc ctg gtg ctc ttc ttc 577
Asp Val Val Leu Pro Val Arg Leu Glu Leu Cys Leu Val Leu Phe Phe
      175              180              185

atc ccc atg gca gtc acc atc ttc tgc tac tgg cgt ttt gtg tgg atc 625
Ile Pro Met Ala Val Thr Ile Phe Cys Tyr Trp Arg Phe Val Trp Ile
      190              195              200              205

atg ctc tcc cag ccc ctt gtg ggg gcc cag agg cgg cgc cga gcc gtg 673
Met Leu Ser Gln Pro Leu Val Gly Ala Gln Arg Arg Arg Arg Ala Val
      210              215              220

ggg ctg gct gtg gtg acg ctg ctc aat ttc ctg gtg tgc ttc gga cct 721
Gly Leu Ala Val Val Thr Leu Leu Asn Phe Leu Val Cys Phe Gly Pro
      225              230              235

tac aac gtg tcc cac ctg gtg ggg tat cac cag aga aaa agc ccc tgg 769
Tyr Asn Val Ser His Leu Val Gly Tyr His Gln Arg Lys Ser Pro Trp
      240              245              250

tgg cgg tca ata gcc gtg gtg ttc agt tca ctc aac gcc agt ctg gac 817
Trp Arg Ser Ile Ala Val Val Phe Ser Ser Leu Asn Ala Ser Leu Asp
      255              260              265

ccc ctg ctc ttc tat ttc tct tct tca gtg gtg cgc agg gca ttt ggg 865
Pro Leu Leu Phe Tyr Phe Ser Ser Ser Val Val Arg Arg Ala Phe Gly
      270              275              280              285

aga ggg ctg cag gtg ctg cgg aat cag ggc tcc tcc ctg ttg gga cgc 913
Arg Gly Leu Gln Val Leu Arg Asn Gln Gly Ser Ser Leu Leu Gly Arg
      290              295              300

aga ggc aaa gac aca gca gag ggg aca aat gag gac agg ggt gtg ggt 961
Arg Gly Lys Asp Thr Ala Glu Gly Thr Asn Glu Asp Arg Gly Val Gly
      305              310              315

caa gga gaa ggg atg cca agt tcy gac ttc act aca gag tag 1003
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cagtttccct 1013

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      20          25          30
Val Gly Arg Ile Arg Gln Pro Gln Pro Ala Pro Val His Ile Leu Leu
      35          40          45
Leu Ser Leu Thr Leu Ala Asp Leu Leu Leu Leu Leu Leu Leu Pro Phe
      50          55          60

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Lys Ile Ile Glu Ala Ala Ser Asn Phe Arg Trp Tyr Leu Pro Lys Val  
 65 70 75 80  
 Val Cys Ala Leu Thr Ser Phe Gly Phe Tyr Ser Ser Ile Tyr Cys Ser  
 85 90 95  
 Thr Trp Leu Leu Ala Gly Ile Ser Ile Glu Arg Tyr Leu Gly Val Ala  
 100 105 110  
 Phe Pro Val Gln Tyr Lys Leu Ser Arg Arg Pro Leu Tyr Gly Val Ile  
 115 120 125  
 Ala Ala Leu Val Ala Trp Val Met Ser Phe Gly His Cys Thr Ile Val  
 130 135 140  
 Ile Ile Val Gln Tyr Leu Asn Thr Thr Glu Gln Val Arg Ser Gly Asn  
 145 150 155 160  
 Glu Ile Thr Cys Tyr Glu Asn Phe Thr Asp Asn Gln Leu Asp Val Val  
 165 170 175  
 Leu Pro Val Arg Leu Glu Leu Cys Leu Val Leu Phe Phe Ile Pro Met  
 180 185 190  
 Ala Val Thr Ile Phe Cys Tyr Trp Arg Phe Val Trp Ile Met Leu Ser  
 195 200 205  
 Gln Pro Leu Val Gly Ala Gln Arg Arg Arg Arg Ala Val Gly Leu Ala  
 210 215 220  
 Val Val Thr Leu Leu Asn Phe Leu Val Cys Phe Gly Pro Tyr Asn Val  
 225 230 235 240  
 Ser His Leu Val Gly Tyr His Gln Arg Lys Ser Pro Trp Trp Arg Ser  
 245 250 255  
 Ile Ala Val Val Phe Ser Ser Leu Asn Ala Ser Leu Asp Pro Leu Leu  
 260 265 270  
 Phe Tyr Phe Ser Ser Ser Val Val Arg Arg Ala Phe Gly Arg Gly Leu  
 275 280 285  
 Gln Val Leu Arg Asn Gln Gly Ser Ser Leu Leu Gly Arg Arg Gly Lys  
 290 295 300  
 Asp Thr Ala Glu Gly Thr Asn Glu Asp Arg Gly Val Gly Gln Gly Glu  
 305 310 315 320  
 Gly Met Pro Ser Ser Asp Phe Thr Thr Glu  
 325 330

<210> 29  
 <211> 1982  
 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (63)...(1460)

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 Met Gly Gly Ala Val Val Asp Glu Gly Pro Thr Gly Val Lys Ala  
 1 5 10 15  
 cct gac ggc ggc tgg ggc tgg gcc gtg ctc ttc ggc tgt ttc gtc atc 155  
 Pro Asp Gly Gly Trp Gly Trp Ala Val Leu Phe Gly Cys Phe Val Ile  
 20 25 30  
 act ggc ttc tcc tac gcc ttc ccc aag gcc gtc agt gtc ttc ttc aag 203  
 Thr Gly Phe Ser Tyr Ala Phe Pro Lys Ala Val Ser Val Phe Phe Lys  
 35 40 45  
 gag ctc ata cag gag ttt ggg atc ggc tac agc gac aca gcc tgg atc 251  
 Glu Leu Ile Gln Glu Phe Gly Ile Gly Tyr Ser Asp Thr Ala Trp Ile

50	55	60	
tcc tcc atc ctg ctg gcc atg ctc tac ggg aca ggt ccg ctc tgc agt Ser Ser Ile Leu Leu Ala Met Leu Tyr Gly Thr Gly Pro Leu Cys Ser 65 70 75			299
gtg tgc gtg aac cgc ttt ggc tgc cgg ccc gtc atg ctt gtg ggg ggt Val Cys Val Asn Arg Phe Gly Cys Arg Pro Val Met Leu Val Gly Gly 80 85 90 95			347
ctc ttt gcg tcg ctg ggc atg gtg gct gcg tcc ttt tgc cgg agc atc Leu Phe Ala Ser Leu Gly Met Val Ala Ala Ser Phe Cys Arg Ser Ile 100 105 110			395
atc cag gtc tac ctc acc act ggg gtc atc acg ggg ttg ggt ttg gca Ile Gln Val Tyr Leu Thr Thr Gly Val Ile Thr Gly Leu Gly Leu Ala 115 120 125			443
ctc aac ttc cag ccc tcg ctc atc atg ctg aac cgc tac ttc agc aag Leu Asn Phe Gln Pro Ser Leu Ile Met Leu Asn Arg Tyr Phe Ser Lys 130 135 140			491
cgg cgc ccc atg gcc aac ggg ctg gcg gca gca ggt agc cct gtc ttc Arg Arg Pro Met Ala Asn Gly Leu Ala Ala Ala Gly Ser Pro Val Phe 145 150 155			539
ctg tgt gcc ctg agc ccg ctg ggg cag ctg ctg cag gac cgc tac ggc Leu Cys Ala Leu Ser Pro Leu Gly Gln Leu Leu Gln Asp Arg Tyr Gly 160 165 170 175			587
tgg cgg ggc ggc ttc ctc atc ctg ggc ggc ctg ctg ctc aac tgc tgc Trp Arg Gly Gly Phe Leu Ile Leu Gly Gly Leu Leu Leu Asn Cys Cys 180 185 190			635
gtg tgt gcc gca ctc atg agg ccc ctg gtg gtc acg gcc cag ccg ggc Val Cys Ala Ala Leu Met Arg Pro Leu Val Val Thr Ala Gln Pro Gly 195 200 205			683
tcg ggg ccg ccg cga ccc tcc cgg cgc ctg cta gac ctg agc gtc ttc Ser Gly Pro Pro Arg Pro Ser Arg Arg Leu Leu Asp Leu Ser Val Phe 210 215 220			731
cgg gac cgc ggc ttt gtg ctt tac gcc gtg gcc gcc tcg gtc atg gtg Arg Asp Arg Gly Phe Val Leu Tyr Ala Val Ala Ala Ser Val Met Val 225 230 235			779
ctg ggg ctc ttc gtc ccg ccc gtg ttc gtg gtg agc tac gcc aag gac Leu Gly Leu Phe Val Pro Pro Val Phe Val Val Ser Tyr Ala Lys Asp 240 245 250 255			827
ctg ggc gtg ccc gac acc aag gcc gcc ttc ctg ctc acc atc ctg ggc Leu Gly Val Pro Asp Thr Lys Ala Ala Phe Leu Leu Thr Ile Leu Gly 260 265 270			875
ttc att gac atc ttc gcg cgg ccg gcc gcg ggc ttc gtg gcg ggg ctt Phe Ile Asp Ile Phe Ala Arg Pro Ala Ala Gly Phe Val Ala Gly Leu 275 280 285			923
ggg aag gtg cgg ccc tac tcc gtc tac ctc ttc agc ttc tcc atg ttc Gly Lys Val Arg Pro Tyr Ser Val Tyr Leu Phe Ser Phe Ser Met Phe 290 295 300			971

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ttc aac ggc ctc gcg gac ctg gcg ggc tct acg gcg ggc gac tac ggc 1019
Phe Asn Gly Leu Ala Asp Leu Ala Gly Ser Thr Ala Gly Asp Tyr Gly
305 310 315

ggc ctc gtg gtc ttc tgc atc ttc ttt ggc atc tcc tac ggc atg gtg 1067
Gly Leu Val Val Phe Cys Ile Phe Phe Gly Ile Ser Tyr Gly Met Val
320 325 330 335

ggg gcc ctg cag ttc gag gtg ctc atg gcc atc gtg ggc acc cac aag 1115
Gly Ala Leu Gln Phe Glu Val Leu Met Ala Ile Val Gly Thr His Lys
340 345 350

ttc tcc agt gcc att ggc ctg gtg ctg ctg atg gag gcg gtg gcc gtg 1163
Phe Ser Ser Ala Ile Gly Leu Val Leu Leu Met Glu Ala Val Ala Val
355 360 365

ctc gtc ggg ccc cct tcg gga ggc aaa ctc ctg gat gcg acc cac gtc 1211
Leu Val Gly Pro Pro Ser Gly Gly Lys Leu Leu Asp Ala Thr His Val
370 375 380

tac atg tac gtg ttc atc ctg gcg ggg gcc gag gtg ctc acc tcc tcc 1259
Tyr Met Tyr Val Phe Ile Leu Ala Gly Ala Glu Val Leu Thr Ser Ser
385 390 395

ctg att ttg ctg ctg ggc aac ttc ttc tgc att agg aag aag ccc aaa 1307
Leu Ile Leu Leu Leu Gly Asn Phe Phe Cys Ile Arg Lys Lys Pro Lys
400 405 410 415

gag cca cag cct gag gtg gcg gcc gcg gag gag gag aag ctc cac aag 1355
Glu Pro Gln Pro Glu Val Ala Ala Ala Glu Glu Glu Lys Leu His Lys
420 425 430

cct cct gca gac tcg ggg gtg gac ttg cgg gag gtg gag cat ttc ctg 1403
Pro Pro Ala Asp Ser Gly Val Asp Leu Arg Glu Val Glu His Phe Leu
435 440 445

aag gct gag cct gag aaa aac ggg gag gtg gtt cac acc ccg gaa aca 1451
Lys Ala Glu Pro Glu Lys Asn Gly Glu Val Val His Thr Pro Glu Thr
450 455 460

agt gtc tga gtggctgggc ggggccggca ggcacaggga ggaggtacag 1500
Ser Val *
465

aagccggcaa cgcttgctat ttattttaca aactggactg gctcaggcag ggccacggct 1560
gggctccagc tgccggccca gcgatcgtc gcccgatcag tgttttgagg gggaaggttg 1620
cggggtggga accgtgtcat tccagagtgg atctgcggtg aagccaagcc gcaaggttac 1680
aaggcatcct caccaggggc cccgcctgct gctcccaggt ggcctgcggc cactgctatg 1740
ctcaaggacc tggaaaccca tgcttcgaga caacgtgact ttaatgggag ggtgggtggg 1800
ccgcagacag gctggcaggg cagggtgctgc gtggggccct ctccagcccg tcctaccctg 1860
ggctcacatg gggcctgtgc ccaccctct tgagtgtctt ggggacagct ctttccaccc 1920
ctggaagatg gaaataaacc tgcgtgtggg tggagtgttc tcgtgccgaa ttcaaaaagc 1980
tt 1982

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&lt;210&gt; 30

&lt;211&gt; 465

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

Met Gly Gly Ala Val Val Asp Glu Gly Pro Thr Gly Val Lys Ala Pro  
 1 5 10 15  
 Asp Gly Gly Trp Gly Trp Ala Val Leu Phe Gly Cys Phe Val Ile Thr  
 20 25 30  
 Gly Phe Ser Tyr Ala Phe Pro Lys Ala Val Ser Val Phe Phe Lys Glu  
 35 40 45  
 Leu Ile Gln Glu Phe Gly Ile Gly Tyr Ser Asp Thr Ala Trp Ile Ser  
 50 55 60  
 Ser Ile Leu Leu Ala Met Leu Tyr Gly Thr Gly Pro Leu Cys Ser Val  
 65 70 75 80  
 Cys Val Asn Arg Phe Gly Cys Arg Pro Val Met Leu Val Gly Gly Leu  
 85 90 95  
 Phe Ala Ser Leu Gly Met Val Ala Ala Ser Phe Cys Arg Ser Ile Ile  
 100 105 110  
 Gln Val Tyr Leu Thr Thr Gly Val Ile Thr Gly Leu Gly Leu Ala Leu  
 115 120 125  
 Asn Phe Gln Pro Ser Leu Ile Met Leu Asn Arg Tyr Phe Ser Lys Arg  
 130 135 140  
 Arg Pro Met Ala Asn Gly Leu Ala Ala Ala Gly Ser Pro Val Phe Leu  
 145 150 155 160  
 Cys Ala Leu Ser Pro Leu Gly Gln Leu Leu Gln Asp Arg Tyr Gly Trp  
 165 170 175  
 Arg Gly Gly Phe Leu Ile Leu Gly Gly Leu Leu Leu Asn Cys Cys Val  
 180 185 190  
 Cys Ala Ala Leu Met Arg Pro Leu Val Val Thr Ala Gln Pro Gly Ser  
 195 200 205  
 Gly Pro Pro Arg Pro Ser Arg Arg Leu Leu Asp Leu Ser Val Phe Arg  
 210 215 220  
 Asp Arg Gly Phe Val Leu Tyr Ala Val Ala Ala Ser Val Met Val Leu  
 225 230 235 240  
 Gly Leu Phe Val Pro Pro Val Phe Val Val Ser Tyr Ala Lys Asp Leu  
 245 250 255  
 Gly Val Pro Asp Thr Lys Ala Ala Phe Leu Leu Thr Ile Leu Gly Phe  
 260 265 270  
 Ile Asp Ile Phe Ala Arg Pro Ala Ala Gly Phe Val Ala Gly Leu Gly  
 275 280 285  
 Lys Val Arg Pro Tyr Ser Val Tyr Leu Phe Ser Phe Ser Met Phe Phe  
 290 295 300  
 Asn Gly Leu Ala Asp Leu Ala Gly Ser Thr Ala Gly Asp Tyr Gly Gly  
 305 310 315 320  
 Leu Val Val Phe Cys Ile Phe Phe Gly Ile Ser Tyr Gly Met Val Gly  
 325 330 335  
 Ala Leu Gln Phe Glu Val Leu Met Ala Ile Val Gly Thr His Lys Phe  
 340 345 350  
 Ser Ser Ala Ile Gly Leu Val Leu Leu Met Glu Ala Val Ala Val Leu  
 355 360 365  
 Val Gly Pro Pro Ser Gly Gly Lys Leu Leu Asp Ala Thr His Val Tyr  
 370 375 380  
 Met Tyr Val Phe Ile Leu Ala Gly Ala Glu Val Leu Thr Ser Ser Leu  
 385 390 395 400  
 Ile Leu Leu Leu Gly Asn Phe Phe Cys Ile Arg Lys Lys Pro Lys Glu  
 405 410 415  
 Pro Gln Pro Glu Val Ala Ala Ala Glu Glu Glu Lys Leu His Lys Pro  
 420 425 430  
 Pro Ala Asp Ser Gly Val Asp Leu Arg Glu Val Glu His Phe Leu Lys  
 435 440 445  
 Ala Glu Pro Glu Lys Asn Gly Glu Val Val His Thr Pro Glu Thr Ser  
 450 455 460  
 Val  
 465

<210> 31  
 <211> 1999  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (53)...(1513)

<400> 31  
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 Met Asp  
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tca tct gtc att caa agg aaa aaa gta gct gtc att ggt ggt ggc ttg 106  
 Ser Ser Val Ile Gln Arg Lys Lys Val Ala Val Ile Gly Gly Gly Leu  
 5 10 15

gtt ggc tca tta caa gca tgc ttt ctt gca aag agg aat ttc cag att 154  
 Val Gly Ser Leu Gln Ala Cys Phe Leu Ala Lys Arg Asn Phe Gln Ile  
 20 25 30

gat gta tat gaa gct agg gaa gat act cga gtg gct acc ttc aca cgt 202  
 Asp Val Tyr Glu Ala Arg Glu Asp Thr Arg Val Ala Thr Phe Thr Arg  
 35 40 45 50

gga aga agc att aac tta gcc ctt tct cat aga gga cga caa gcc ttg 250  
 Gly Arg Ser Ile Asn Leu Ala Leu Ser His Arg Gly Arg Gln Ala Leu  
 55 60 65

aaa gct gtt ggc ctg gaa gat cag att gta tcc caa ggt att ccc atg 298  
 Lys Ala Val Gly Leu Glu Asp Gln Ile Val Ser Gln Gly Ile Pro Met  
 70 75 80

aga gca aga atg atc cac tct ctt tca gga aaa aag tct gca att ccc 346  
 Arg Ala Arg Met Ile His Ser Leu Ser Gly Lys Lys Ser Ala Ile Pro  
 85 90 95

tat ggg aca aag tct cag tat att ctt tct gta agc aga gaa aat cta 394  
 Tyr Gly Thr Lys Ser Gln Tyr Ile Leu Ser Val Ser Arg Glu Asn Leu  
 100 105 110

aac aag gat cta ttg act gct gct gag aaa tac ccc aat gtg aaa atg 442  
 Asn Lys Asp Leu Leu Thr Ala Ala Glu Lys Tyr Pro Asn Val Lys Met  
 115 120 125 130

cac ttt aac cac agg ctg ttg aaa tgt aat cca gag gaa gga atg atc 490  
 His Phe Asn His Arg Leu Leu Lys Cys Asn Pro Glu Glu Gly Met Ile  
 135 140 145

aca gtg ctt gga tct gac aaa gtt ccc aaa gat gtc act tgt gac ctc 538  
 Thr Val Leu Gly Ser Asp Lys Val Pro Lys Asp Val Thr Cys Asp Leu  
 150 155 160

att gta gga tgt gat gga gcc tat tca act gtc aga tct cac ctg atg 586  
 Ile Val Gly Cys Asp Gly Ala Tyr Ser Thr Val Arg Ser His Leu Met  
 165 170 175

aag aaa cct cgc ttt gat tac agt cag cag tac att cct cat ggg tac 634  
 Lys Lys Pro Arg Phe Asp Tyr Ser Gln Gln Tyr Ile Pro His Gly Tyr



180	185	190	
atg gag ttg act att cca cct aag aac gga gat tat gcc atg gaa cct			682
Met Glu Leu Thr Ile Pro Pro Lys Asn Gly Asp Tyr Ala Met Glu Pro			
195	200	205	210
aat tat ctg cat att tgg cct aga aat acc ttt atg atg att gca ctt			730
Asn Tyr Leu His Ile Trp Pro Arg Asn Thr Phe Met Met Ile Ala Leu			
	215	220	225
cct aac atg aac aaa tca ttc aca tgt act ttg ttc atg ccc ttt gaa			778
Pro Asn Met Lys Ser Phe Thr Cys Thr Leu Phe Met Pro Phe Glu			
	230	235	240
gag ttt gaa aaa ctt cta acc agt aat gat gtg gta gat ttc ttc cag			826
Glu Phe Glu Lys Leu Leu Thr Ser Asn Asp Val Val Asp Phe Phe Gln			
	245	250	255
aaa tac ttt ccg gat gcc atc cct cta att gga gag aaa ctc cta gtg			874
Lys Tyr Phe Pro Asp Ala Ile Pro Leu Ile Gly Glu Lys Leu Leu Val			
	260	265	270
caa gat ttc ttc ctg ttg cct gcc cag ccc atg ata tct gta aag tgc			922
Gln Asp Phe Phe Leu Leu Pro Ala Gln Pro Met Ile Ser Val Lys Cys			
	275	280	285
tct tca ttt cac ttt aaa tct cac tgt gta ctg ctg gga gat gca gct			970
Ser Ser Phe His Phe Lys Ser His Cys Val Leu Leu Gly Asp Ala Ala			
	295	300	305
cat gct ata gtg ccg ttt ttt ggg caa gga atg aat gcg ggc ttt gaa			1018
His Ala Ile Val Pro Phe Phe Gly Gln Gly Met Asn Ala Gly Phe Glu			
	310	315	320
gac tgc ttg gta ttt gat gag tta atg gat aaa ttc agt aac gac ctt			1066
Asp Cys Leu Val Phe Asp Glu Leu Met Asp Lys Phe Ser Asn Asp Leu			
	325	330	335
agt ttg tgt ctt cct gtg ttc tca aga ttg aga atc cca gat gat cac			1114
Ser Leu Cys Leu Pro Val Phe Ser Arg Leu Arg Ile Pro Asp Asp His			
	340	345	350
gcg att tca gac cta tcc atg tac aat tac ata gag atg cga gca cat			1162
Ala Ile Ser Asp Leu Ser Met Tyr Asn Tyr Ile Glu Met Arg Ala His			
	355	360	365
gtc aac tca agc tgg ttc att ttt cag aag aac atg gag aga ttt ctt			1210
Val Asn Ser Ser Trp Phe Ile Phe Gln Lys Asn Met Glu Arg Phe Leu			
	375	380	385
cat gcg att atg cca tcg acc ttt atc cct ctc tat aca atg gtc act			1258
His Ala Ile Met Pro Ser Thr Phe Ile Pro Leu Tyr Thr Met Val Thr			
	390	395	400
ttt tcc aga ata aga tac cat gag gct gtg cag cgt tgg cat tgg caa			1306
Phe Ser Arg Ile Arg Tyr His Glu Ala Val Gln Arg Trp His Trp Gln			
	405	410	415
aaa aag gtg ata aac aaa gga ctc ttt ttc ttg gga tca ctg ata gcc			1354
Lys Lys Val Ile Asn Lys Gly Leu Phe Phe Leu Gly Ser Leu Ile Ala			
	420	425	430

atc agc agt acc tac cta ctt ata cac tac atg tca cca cga tct ttc 1402  
 Ile Ser Ser Thr Tyr Leu Leu Ile His Tyr Met Ser Pro Arg Ser Phe  
 435 440 445 450

ctc tgc ttg aga aga cca tgg aac tgg ata gct cac ttc cgg aat aca 1450  
 Leu Cys Leu Arg Arg Pro Trp Asn Trp Ile Ala His Phe Arg Asn Thr  
 455 460 465

aca tgt ttc ccc gca aag gcc gtg gac tcc cta gaa caa att tcc aat 1498  
 Thr Cys Phe Pro Ala Lys Ala Val Asp Ser Leu Glu Gln Ile Ser Asn  
 470 475 480

ctc att agc agg tga tagaaagggtt ttgtggtagc aaatgcatga tttctctgtg 1553  
 Leu Ile Ser Arg \*  
 485

acccaaatta agcatgaaaa aaatgtttcc attgccatat ttgattcact agtgggaagat 1613  
 agtgttctgc ttataattaa actgaatgta gatatctct gtatgttaat tgcaattact 1673  
 ggttgggggg tgcatttttaa aagatgaaac atgcagcttc cctacattac acacactcag 1733  
 gttgagtcac tctaactata aaagtgcatt gactaagatc cttcacttct ctgaaagtaa 1793  
 ggccctagat gcctcaggga agacagtaat catgcctttt ctttaaaaga cacaatagga 1853  
 ctgcgaacag cattgactca acacctagga ctaaaaatca caacttaact agcatgttaa 1913  
 ctgcactttt cattacgtga atggaactta cctaaccaca gggctcagac ttactagata 1973  
 aaaccagaaa tggaaataag gaattc 1999

<210> 32

<211> 486

<212> PRT

<213> Homo sapiens

<400> 32

Met Asp Ser Ser Val Ile Gln Arg Lys Lys Val Ala Val Ile Gly Gly  
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 Gly Leu Val Gly Ser Leu Gln Ala Cys Phe Leu Ala Lys Arg Asn Phe  
 20 25 30  
 Gln Ile Asp Val Tyr Glu Ala Arg Glu Asp Thr Arg Val Ala Thr Phe  
 35 40 45  
 Thr Arg Gly Arg Ser Ile Asn Leu Ala Leu Ser His Arg Gly Arg Gln  
 50 55 60  
 Ala Leu Lys Ala Val Gly Leu Glu Asp Gln Ile Val Ser Gln Gly Ile  
 65 70 75 80  
 Pro Met Arg Ala Arg Met Ile His Ser Leu Ser Gly Lys Lys Ser Ala  
 85 90 95  
 Ile Pro Tyr Gly Thr Lys Ser Gln Tyr Ile Leu Ser Val Ser Arg Glu  
 100 105 110  
 Asn Leu Asn Lys Asp Leu Leu Thr Ala Ala Glu Lys Tyr Pro Asn Val  
 115 120 125  
 Lys Met His Phe Asn His Arg Leu Leu Lys Cys Asn Pro Glu Glu Gly  
 130 135 140  
 Met Ile Thr Val Leu Gly Ser Asp Lys Val Pro Lys Asp Val Thr Cys  
 145 150 155 160  
 Asp Leu Ile Val Gly Cys Asp Gly Ala Tyr Ser Thr Val Arg Ser His  
 165 170 175  
 Leu Met Lys Lys Pro Arg Phe Asp Tyr Ser Gln Gln Tyr Ile Pro His  
 180 185 190  
 Gly Tyr Met Glu Leu Thr Ile Pro Pro Lys Asn Gly Asp Tyr Ala Met  
 195 200 205  
 Glu Pro Asn Tyr Leu His Ile Trp Pro Arg Asn Thr Phe Met Met Ile  
 210 215 220  
 Ala Leu Pro Asn Met Asn Lys Ser Phe Thr Cys Thr Leu Phe Met Pro

[illegible]

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<210> 33
<211> 5415
<212> DNA
<213> Homo sapiens
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<220>  
<221> CDS  
<222> (173)...(3739)
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<400> 33
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gccggggggag tccgctagcg cacgcgtgcc cccgagtcgc cgtccgcgca cg atg ggg 178
                                         Met Gly
                                         1

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cac ctg ccc acg ggg ata cac ggc gcc cgc cgc ctc ctg cct ctg ctc 226  
 His Leu Pro Thr Gly Ile His Gly Ala Arg Arg Leu Leu Pro Leu Leu  
           5                          10                          15

tgg ctc ttt gtg ctg ttc aag aat gct aca gct ttc cat gta act gtc 274  
 Trp Leu Phe Val Leu Phe Lys Asn Ala Thr Ala Phe His Val Thr Val  
 20 25 30

caa gat gat aat aac atc gtt gtc tca tta gaa gct tca gac gtc atc 322  
Gln Asp Asp Asn Asn Ile Val Val Ser Leu Glu Ala Ser Asp Val Ile

35	40	45	50	
agt cca gca tct gtg tat gtt gtg aag ata act ggt gaa tcc aaa aat				370
Ser Pro Ala Ser Val Tyr Val Val Lys Ile Thr Gly Glu Ser Lys Asn	55	60	65	
tat ttc ttc gaa ttt gag gaa ttc aac agc act ttg cct cct cct gtt				418
Tyr Phe Phe Glu Phe Glu Glu Phe Asn Ser Thr Leu Pro Pro Pro Val	70	75	80	
att ttc aag gcc agt tat cat ggc ctt tat tat ata atc act ctg gta				466
Ile Phe Lys Ala Ser Tyr His Gly Leu Tyr Tyr Ile Ile Thr Leu Val	85	90	95	
gtg gta aat gga aat gtg gtg acc aag cca tcc aga tca atc act gtg				514
Val Val Asn Gly Asn Val Thr Lys Pro Ser Arg Ser Ile Thr Val	100	105	110	
tta aca aaa cct cta cct gta acc agt gtt tcc ata tat gac tat aaa				562
Leu Thr Lys Pro Leu Pro Val Thr Ser Val Ser Ile Tyr Asp Tyr Lys	115	120	125	130
cct tct cct gaa aca gga gtc ctg ttt gaa ata cat tat cca gaa aaa				610
Pro Ser Pro Glu Thr Gly Val Leu Phe Glu Ile His Tyr Pro Glu Lys	135	140	145	
tat aac gtt ttc aca aga gtg aac att agc tac tgg gaa ggt aaa gac				658
Tyr Asn Val Phe Thr Arg Val Asn Ile Ser Tyr Trp Glu Gly Lys Asp	150	155	160	
ttc cgg aca atg cta tat aaa gat ttc ttt aag gga aaa aca gta ttt				706
Phe Arg Thr Met Leu Tyr Lys Asp Phe Phe Lys Gly Lys Thr Val Phe	165	170	175	
aat cac tgg ctg cca gga atg tgt tat agt aat atc acc ttt cag ctg				754
Asn His Trp Leu Pro Gly Met Cys Tyr Ser Asn Ile Thr Phe Gln Leu	180	185	190	
gta tct gag gca act ttt aat aaa agt acc ctt gtt gag tac agt ggt				802
Val Ser Glu Ala Thr Phe Asn Lys Ser Thr Leu Val Glu Tyr Ser Gly	195	200	205	210
gtc agt cac gaa ccc aaa cag cac aga act gcc cct tat cca cct caa				850
Val Ser His Glu Pro Lys Gln His Arg Thr Ala Pro Tyr Pro Pro Gln	215	220	225	
aat att tcc gtt cgt atc gta aac ttg aac aaa aac aac tgg gaa gaa				898
Asn Ile Ser Val Arg Ile Val Asn Leu Asn Lys Asn Asn Trp Glu Glu	230	235	240	
cag agt ggc aat ttc cca gaa gaa tcc ttc atg aga tca caa gat aca				946
Gln Ser Gly Asn Phe Pro Glu Glu Ser Phe Met Arg Ser Gln Asp Thr	245	250	255	
ata gga aaa gaa aaa ctc ttc cat ttt aca gaa gaa acc cct gaa att				994
Ile Gly Lys Glu Lys Leu Phe His Phe Thr Glu Glu Thr Pro Glu Ile	260	265	270	
ccc tcg ggc aac att tct tcc ggt tgg cct gat ttt aat agc agt gac				1042
Pro Ser Gly Asn Ile Ser Ser Gly Trp Pro Asp Phe Asn Ser Ser Asp	275	280	285	290

tat gaa act acg tct cag cca tat tgg tgg gac agt gca tct gca gct	1090
Tyr Glu Thr Thr Ser Gln Pro Tyr Trp Trp Asp Ser Ala Ser Ala Ala	
295 300 305	
cct gaa agt gaa gat gaa ttt gtc agc gta ctt ccc atg gaa tac gaa	1138
Pro Glu Ser Glu Asp Glu Phe Val Ser Val Leu Pro Met Glu Tyr Glu	
310 315 320	
aat aac agt aca ctc agt gag aca gag aag tca aca tca ggc tct ttc	1186
Asn Asn Ser Thr Leu Ser Glu Thr Glu Lys Ser Thr Ser Gly Ser Phe	
325 330 335	
tcc ttt ttc cct gtg caa atg ata ttg acc tgg tta cca ccc aaa cca	1234
Ser Phe Phe Pro Val Gln Met Ile Leu Thr Trp Leu Pro Pro Lys Pro	
340 345 350	
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Pro Thr Ala Phe Asp Gly Phe His Ile His Ile Glu Arg Glu Glu Asn	
355 360 365 370	
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Phe Thr Glu Tyr Leu Met Val Asp Glu Glu Ala His Glu Phe Val Ala	
375 380 385	
gaa ctg aag gaa cct ggg aaa tat aag tta tct gtg aca acc ttt agt	1378
Glu Leu Lys Glu Pro Gly Lys Tyr Lys Leu Ser Val Thr Thr Phe Ser	
390 395 400	
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Ser Ser Gly Ser Cys Glu Thr Arg Lys Ser Gln Ser Ala Lys Ser Leu	
405 410 415	
agc ttt tat atc agt cct tca gga gag tgg att gaa gaa ctg acc gag	1474
Ser Phe Tyr Ile Ser Pro Ser Gly Glu Trp Ile Glu Glu Leu Thr Glu	
420 425 430	
aag ccg cag cac gtg agt gtc cac gtt tta agc tca acc act gcc ttg	1522
Lys Pro Gln His Val Ser Val His Val Leu Ser Ser Thr Thr Ala Leu	
435 440 445 450	
atg tcc tgg aca tct tcc caa gag aac tac aac agc acc att gtg tct	1570
Met Ser Trp Thr Ser Ser Gln Glu Asn Tyr Asn Ser Thr Ile Val Ser	
455 460 465	
gtg gtg tcg ctg acc tgc cag aaa caa aag gag agc cag agg ctt gaa	1618
Val Val Ser Leu Thr Cys Gln Lys Gln Lys Glu Ser Gln Arg Leu Glu	
470 475 480	
aag cag tac tgc act cag gtg aac tca agc aaa cct att att gaa aat	1666
Lys Gln Tyr Cys Thr Gln Val Asn Ser Ser Lys Pro Ile Ile Glu Asn	
485 490 495	
ctg gtt cct ggt gcc cag tac cag gtt gta ata tac cta agg aaa ggc	1714
Leu Val Pro Gly Ala Gln Tyr Gln Val Val Ile Tyr Leu Arg Lys Gly	
500 505 510	
cct ttg att gga cca cct tca gat cct gtg aca ttt gct att gtt ccc	1762
Pro Leu Ile Gly Pro Pro Ser Asp Pro Val Thr Phe Ala Ile Val Pro	
515 520 525 530	

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gtt ctg agc tgg acc aga cct tat tta ggc gtg ttc aga aaa tac gtg Val Leu Ser Trp Thr Arg Pro Tyr Leu Gly Val Phe Arg Lys Tyr Val 550 555 560	1858
gtt gaa atg ttt tat ttc aac cct gct aca atg aca tca gag tgg acc Val Glu Met Phe Tyr Phe Asn Pro Ala Thr Met Thr Ser Glu Trp Thr 565 570 575	1906
acc tac tat gaa ata gca gca act gtt tcc tta act gca tcc gtg aga Thr Tyr Tyr Glu Ile Ala Ala Thr Val Ser Leu Thr Ala Ser Val Arg 580 585 590	1954
ata gct aat ctg ctg cca gca tgg tac tac aac ttc cgg gtt acc atg Ile Ala Asn Leu Leu Pro Ala Trp Tyr Tyr Asn Phe Arg Val Thr Met 595 600 605 610	2002
gtg acg tgg gga gat cca gaa ttg agc tgc tgt gac agc tct acc atc Val Thr Trp Gly Asp Pro Glu Leu Ser Cys Cys Asp Ser Ser Thr Ile 615 620 625	2050
agc ttc ata aca gcc cca gtg gct ccg gaa atc act tct gtg gaa tat Ser Phe Ile Thr Ala Pro Val Ala Pro Glu Ile Thr Ser Val Glu Tyr 630 635 640	2098
ttc aac agt ctg tta tat atc agt tgg aca tat ggg gat gat aca acg Phe Asn Ser Leu Leu Tyr Ile Ser Trp Thr Tyr Gly Asp Asp Thr Thr 645 650 655	2146
gac ttg tcc cat tct aga atg ctt cac tgg atg gtg gtt gca gaa gga Asp Leu Ser His Ser Arg Met Leu His Trp Met Val Val Ala Glu Gly 660 665 670	2194
aaa aag aaa att aaa aag agt gta aca cgc aat gtc atg act gca att Lys Lys Lys Ile Lys Lys Ser Val Thr Arg Asn Val Met Thr Ala Ile 675 680 685 690	2242
ctc agc ttg cct cca ggc gac atc tat aac ctc tca gta act gct tgt Leu Ser Leu Pro Pro Gly Asp Ile Tyr Asn Leu Ser Val Thr Ala Cys 695 700 705	2290
act gaa aga gga agt aat acc tcc atg ctc cgc ctt gtc aag cta gaa Thr Glu Arg Gly Ser Asn Thr Ser Met Leu Arg Leu Val Lys Leu Glu 710 715 720	2338
cca gct cca ccc aaa tca ctc ttc gca gtg aac aaa acc cag act tca Pro Ala Pro Pro Lys Ser Leu Phe Ala Val Asn Lys Thr Gln Thr Ser 725 730 735	2386
gtg act ttg ctg tgg gtg gaa gag gga gta gct gat ttc ttt gaa gtt Val Thr Leu Leu Trp Val Glu Gly Val Ala Asp Phe Phe Glu Val 740 745 750	2434
ttc tgt caa caa gtt ggc tcc agt cag aaa acc aaa ctt cag gaa cca Phe Cys Gln Gln Val Gly Ser Ser Gln Lys Thr Lys Leu Gln Glu Pro 755 760 765 770	2482
gtt gct gtt tct tcc cat gtc gtg acc atc tcc agc ctt ctt cct gcc	2530

Val Ala Val Ser Ser His Val Val Thr Ile Ser Ser Leu Leu Pro Ala	
775 780 785	
act gcc tac aat tgt agt gtc acc agc ttt agc cat gac agc ccc agt	2578
Thr Ala Tyr Asn Cys Ser Val Thr Ser Phe Ser His Asp Ser Pro Ser	
790 795 800	
gtc cct acg ttc ata gcc gtc tca aca atg gtt aca gag atg aat ccc	2626
Val Pro Thr Phe Ile Ala Val Ser Thr Met Val Thr Glu Met Asn Pro	
805 810 815	
aat gtg gta gtg atc tcc gtg ctg gcc atc ctt agc aca ctt tta att	2674
Asn Val Val Val Ile Ser Val Leu Ala Ile Leu Ser Thr Leu Leu Ile	
820 825 830	
gga ctg ttg ctt gtt acc ctg att att ctt agg aaa aag cat ctg cag	2722
Gly Leu Leu Leu Val Thr Leu Ile Ile Leu Arg Lys Lys His Leu Gln	
835 840 845 850	
atg gct agg gag tgt gga gct ggt aca ttt gtc aat ttt gca tcc tta	2770
Met Ala Arg Glu Cys Gly Ala Gly Thr Phe Val Asn Phe Ala Ser Leu	
855 860 865	
gag agg gat gga aag ctt cca tac aac tgg agt aaa aat ggt tta aag	2818
Glu Arg Asp Gly Lys Leu Pro Tyr Asn Trp Ser Lys Asn Gly Leu Lys	
870 875 880	
aag agg aaa ctg aca aac ccg gtt caa ctg gat gac ttt gat gcc tat	2866
Lys Arg Lys Leu Thr Asn Pro Val Gln Leu Asp Asp Phe Asp Ala Tyr	
885 890 895	
att aag gat atg gcc aaa gac tct gac tat aaa ttt tct ctt cag ttt	2914
Ile Lys Asp Met Ala Lys Asp Ser Asp Tyr Lys Phe Ser Leu Gln Phe	
900 905 910	
gag gag ttg aaa ttg att gga ctg gat atc cca cac ttt gct gca gat	2962
Glu Glu Leu Lys Leu Ile Gly Leu Asp Ile Pro His Phe Ala Ala Asp	
915 920 925 930	
ctt cca ctg aat cga tgt aaa aac cgt tac aca aac atc cta cca tat	3010
Leu Pro Leu Asn Arg Cys Lys Asn Arg Tyr Thr Asn Ile Leu Pro Tyr	
935 940 945	
gac ttc agc cgt gtg aga tta gtc tcc atg aat gaa gag gaa ggt gca	3058
Asp Phe Ser Arg Val Arg Leu Val Ser Met Asn Glu Glu Glu Gly Ala	
950 955 960	
gac tac atc aat gcc aac tat att cct gga tac aac tca ccc cag gag	3106
Asp Tyr Ile Asn Ala Asn Tyr Ile Pro Gly Tyr Asn Ser Pro Gln Glu	
965 970 975	
tat att gcc acc cag ggg cca ctg cct gaa acc aga aat gac ttc tgg	3154
Tyr Ile Ala Thr Gln Gly Pro Leu Pro Glu Thr Arg Asn Asp Phe Trp	
980 985 990	
aag atg gtc ctg caa caa aag tct cag att att gtc atg ctg act cag	3202
Lys Met Val Leu Gln Gln Lys Ser Gln Ile Ile Val Met Leu Thr Gln	
995 1000 1005 1010	
tgt aat gag aaa agg agg gtg aaa tgt gac cat tac tgg cca ttc acg	3250
Cys Asn Glu Lys Arg Arg Val Lys Cys Asp His Tyr Trp Pro Phe Thr	

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 Glu Glu Pro Ile Ala Tyr Gly Asp Ile Thr Val Glu Met Ile Ser Glu  
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 His Gly Val Pro Thr Ala Asn Ala Ala Glu Ser Ile Leu Gln Phe Val  
 1075 1080 1085 1090  
 cac atg gtc cga cag caa gct acc aag agc aaa ggt ccc atg atc att 3490  
 His Met Val Arg Gln Gln Ala Thr Lys Ser Lys Gly Pro Met Ile Ile  
 1095 1100 1105  
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 His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Ile Ala Leu Asp  
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 agg ctc ttg cag cac att cgg gat cat gag ttt gtt gac atc tta ggg 3586  
 Arg Leu Leu Gln His Ile Arg Asp His Glu Phe Val Asp Ile Leu Gly  
 1125 1130 1135  
 ctg gtg tca gaa atg agg tca tac cgg atg tct atg gta cag aca gag 3634  
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 1140 1145 1150  
 gag cag tac att ttt atc cat cag tgt gtg caa ctg atg tgg atg aag 3682  
 Glu Gln Tyr Ile Phe Ile His Gln Cys Val Gln Leu Met Trp Met Lys  
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 Lys Lys Gln Gln Phe Cys Ile Ser Asp Val Ile Tyr Glu Asn Val Ser  
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 aag tcc tag ttcagaatcc ggagcagaga ggacatgatg tgcgcccac 3779  
 Lys Ser \*

ctcccttgc tccagattgt tttagtgggc cctgatggtc atttttctaa acagaggccc 3839  
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tcaacctcgc ttcccc 5415

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&lt;210&gt; 34

&lt;211&gt; 1188

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 34

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Leu Leu Trp Leu Phe Val Leu Phe Lys Asn Ala Thr Ala Phe His Val
20     25     30
Thr Val Gln Asp Asp Asn Asn Ile Val Val Ser Leu Glu Ala Ser Asp
35     40     45
Val Ile Ser Pro Ala Ser Val Tyr Val Val Lys Ile Thr Gly Glu Ser
50     55     60
Lys Asn Tyr Phe Phe Glu Phe Glu Glu Phe Asn Ser Thr Leu Pro Pro
65     70     75     80
Pro Val Ile Phe Lys Ala Ser Tyr His Gly Leu Tyr Tyr Ile Ile Thr
85     90     95
Leu Val Val Val Asn Gly Asn Val Val Thr Lys Pro Ser Arg Ser Ile
100    105    110
Thr Val Leu Thr Lys Pro Leu Pro Val Thr Ser Val Ser Ile Tyr Asp
115    120    125
Tyr Lys Pro Ser Pro Glu Thr Gly Val Leu Phe Glu Ile His Tyr Pro
130    135    140
Glu Lys Tyr Asn Val Phe Thr Arg Val Asn Ile Ser Tyr Trp Glu Gly
145    150    155    160
Lys Asp Phe Arg Thr Met Leu Tyr Lys Asp Phe Phe Lys Gly Lys Thr
165    170    175
Val Phe Asn His Trp Leu Pro Gly Met Cys Tyr Ser Asn Ile Thr Phe
180    185    190
Gln Leu Val Ser Glu Ala Thr Phe Asn Lys Ser Thr Leu Val Glu Tyr
195    200    205
Ser Gly Val Ser His Glu Pro Lys Gln His Arg Thr Ala Pro Tyr Pro
210    215    220
Pro Gln Asn Ile Ser Val Arg Ile Val Asn Leu Asn Lys Asn Asn Trp
225    230    235    240
Glu Glu Gln Ser Gly Asn Phe Pro Glu Glu Ser Phe Met Arg Ser Gln
245    250    255
Asp Thr Ile Gly Lys Glu Lys Leu Phe His Phe Thr Glu Glu Thr Pro
260    265    270
Glu Ile Pro Ser Gly Asn Ile Ser Ser Gly Trp Pro Asp Phe Asn Ser
275    280    285
Ser Asp Tyr Glu Thr Thr Ser Gln Pro Tyr Trp Trp Asp Ser Ala Ser
290    295    300
Ala Ala Pro Glu Ser Glu Asp Glu Phe Val Ser Val Leu Pro Met Glu
305    310    315    320
Tyr Glu Asn Asn Ser Thr Leu Ser Glu Thr Glu Lys Ser Thr Ser Gly

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325 330 335  
 Ser Phe Ser Phe Phe Pro Val Gln Met Ile Leu Thr Trp Leu Pro Pro  
 340 345 350  
 Lys Pro Pro Thr Ala Phe Asp Gly Phe His Ile His Ile Glu Arg Glu  
 355 360 365  
 Glu Asn Phe Thr Glu Tyr Leu Met Val Asp Glu Glu Ala His Glu Phe  
 370 375 380  
 Val Ala Glu Leu Lys Glu Pro Gly Lys Tyr Lys Leu Ser Val Thr Thr  
 385 390 395 400  
 Phe Ser Ser Ser Gly Ser Cys Glu Thr Arg Lys Ser Gln Ser Ala Lys  
 405 410 415  
 Ser Leu Ser Phe Tyr Ile Ser Pro Ser Gly Glu Trp Ile Glu Glu Leu  
 420 425 430  
 Thr Glu Lys Pro Gln His Val Ser Val His Val Leu Ser Ser Thr Thr  
 435 440 445  
 Ala Leu Met Ser Trp Thr Ser Ser Gln Glu Asn Tyr Asn Ser Thr Ile  
 450 455 460  
 Val Ser Val Val Ser Leu Thr Cys Gln Lys Gln Lys Glu Ser Gln Arg  
 465 470 475 480  
 Leu Glu Lys Gln Tyr Cys Thr Gln Val Asn Ser Ser Lys Pro Ile Ile  
 485 490 495  
 Glu Asn Leu Val Pro Gly Ala Gln Tyr Gln Val Val Ile Tyr Leu Arg  
 500 505 510  
 Lys Gly Pro Leu Ile Gly Pro Pro Ser Asp Pro Val Thr Phe Ala Ile  
 515 520 525  
 Val Pro Thr Gly Ile Lys Asp Leu Met Leu Tyr Pro Leu Gly Pro Thr  
 530 535 540  
 Ala Val Val Leu Ser Trp Thr Arg Pro Tyr Leu Gly Val Phe Arg Lys  
 545 550 555 560  
 Tyr Val Val Glu Met Phe Tyr Phe Asn Pro Ala Thr Met Thr Ser Glu  
 565 570 575  
 Trp Thr Thr Tyr Tyr Glu Ile Ala Ala Thr Val Ser Leu Thr Ala Ser  
 580 585 590  
 Val Arg Ile Ala Asn Leu Leu Pro Ala Trp Tyr Tyr Asn Phe Arg Val  
 595 600 605  
 Thr Met Val Thr Trp Gly Asp Pro Glu Leu Ser Cys Cys Asp Ser Ser  
 610 615 620  
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 625 630 635 640  
 Glu Tyr Phe Asn Ser Leu Leu Tyr Ile Ser Trp Thr Tyr Gly Asp Asp  
 645 650 655  
 Thr Thr Asp Leu Ser His Ser Arg Met Leu His Trp Met Val Ala  
 660 665 670  
 Glu Gly Lys Lys Lys Ile Lys Lys Ser Val Thr Arg Asn Val Met Thr  
 675 680 685  
 Ala Ile Leu Ser Leu Pro Pro Gly Asp Ile Tyr Asn Leu Ser Val Thr  
 690 695 700  
 Ala Cys Thr Glu Arg Gly Ser Asn Thr Ser Met Leu Arg Leu Val Lys  
 705 710 715 720  
 Leu Glu Pro Ala Pro Lys Ser Leu Phe Ala Val Asn Lys Thr Gln  
 725 730 735  
 Thr Ser Val Thr Leu Leu Trp Val Glu Glu Gly Val Ala Asp Phe Phe  
 740 745 750  
 Glu Val Phe Cys Gln Gln Val Gly Ser Ser Gln Lys Thr Lys Leu Gln  
 755 760 765  
 Glu Pro Val Ala Val Ser Ser His Val Val Thr Ile Ser Ser Leu Leu  
 770 775 780  
 Pro Ala Thr Ala Tyr Asn Cys Ser Val Thr Ser Phe Ser His Asp Ser  
 785 790 795 800  
 Pro Ser Val Pro Thr Phe Ile Ala Val Ser Thr Met Val Thr Glu Met  
 805 810 815

Asn Pro Asn Val Val Val Ile Ser Val Leu Ala Ile Leu Ser Thr Leu  
 820 825 830  
 Leu Ile Gly Leu Leu Leu Val Thr Leu Ile Ile Leu Arg Lys Lys His  
 835 840 845  
 Leu Gln Met Ala Arg Glu Cys Gly Ala Gly Thr Phe Val Asn Phe Ala  
 850 855 860  
 Ser Leu Glu Arg Asp Gly Lys Leu Pro Tyr Asn Trp Ser Lys Asn Gly  
 865 870 875 880  
 Leu Lys Lys Arg Lys Leu Thr Asn Pro Val Gln Leu Asp Asp Phe Asp  
 885 890 895  
 Ala Tyr Ile Lys Asp Met Ala Lys Asp Ser Asp Tyr Lys Phe Ser Leu  
 900 905 910  
 Gln Phe Glu Glu Leu Lys Leu Ile Gly Leu Asp Ile Pro His Phe Ala  
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 Ala Asp Leu Pro Leu Asn Arg Cys Lys Asn Arg Tyr Thr Asn Ile Leu  
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 Pro Tyr Asp Phe Ser Arg Val Arg Leu Val Ser Met Asn Glu Glu Glu  
 945 950 955 960  
 Gly Ala Asp Tyr Ile Asn Ala Asn Tyr Ile Pro Gly Tyr Asn Ser Pro  
 965 970 975  
 Gln Glu Tyr Ile Ala Thr Gln Gly Pro Leu Pro Glu Thr Arg Asn Asp  
 980 985 990  
 Phe Trp Lys Met Val Leu Gln Gln Lys Ser Gln Ile Ile Val Met Leu  
 995 1000 1005  
 Thr Gln Cys Asn Glu Lys Arg Arg Val Lys Cys Asp His Tyr Trp Pro  
 1010 1015 1020  
 Phe Thr Glu Glu Pro Ile Ala Tyr Gly Asp Ile Thr Val Glu Met Ile  
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 1045 1050 1055  
 Tyr Ala Asp Glu Met Gln Asp Val Met His Phe Asn Tyr Thr Ala Trp  
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 1075 1080 1085  
 Phe Val His Met Val Arg Gln Gln Ala Thr Lys Ser Lys Gly Pro Met  
 1090 1095 1100  
 Ile Ile His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Ile Ala  
 1105 1110 1115 1120  
 Leu Asp Arg Leu Leu Gln His Ile Arg Asp His Glu Phe Val Asp Ile  
 1125 1130 1135  
 Leu Gly Leu Val Ser Glu Met Arg Ser Tyr Arg Met Ser Met Val Gln  
 1140 1145 1150  
 Thr Glu Glu Gln Tyr Ile Phe Ile His Gln Cys Val Gln Leu Met Trp  
 1155 1160 1165  
 Met Lys Lys Lys Gln Gln Phe Cys Ile Ser Asp Val Ile Tyr Glu Asn  
 1170 1175 1180  
 Val Ser Lys Ser  
 1185

&lt;210&gt; 35

&lt;211&gt; 2373

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (6)...(2129)

&lt;400&gt; 35

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Cys Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe  
20 25 30

cct gga gac ctg aga acc aat ctc acc gac agg cag ctg gca gag gaa 146  
Pro Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu  
35 40 45

tac ctg tac cgc tat ggt tac act cgg gtg gca gag atg cgt gga gag 194  
Tyr Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu  
50 55 60

tgc aaa tct ctg ggg cct gcg ctg ctg ctt ctc cag aag caa ctg tcc 242  
Ser Lys Ser Leu Gly Pro Ala Leu Leu Leu Gln Lys Gln Leu Ser  
65 70 75

ctg ccc gag acc ggt gag ctg gat agc gcc acg ctg aag gcc atg cga 290  
Leu Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg  
80 85 90 95

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Thr Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu  
100 105 110

ggc gac ctc aag tgg cac cac cac aac atc acc tat tgg atc caa aac 386  
Gly Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn  
115 120 125

tac tgc gaa gac ttg ccg cgg gcg gtg att gac gac gcc ttt gcc cgc 434  
Tyr Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg  
130 135 140

gcc ttc gca ctg tgg agc gcg gtg acg ccg ctc acc ttc act cgc gtg 482  
Ala Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val  
145 150 155

tac agc cgg gac gca gac atc gtc atc cag ttt ggt gtc gcg gag cac 530  
Tyr Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His  
160 165 170 175

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Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala  
180 185 190

ttt cct cct ggc ccc ggc att cag gga gac gcc cat ttc gac gat gac 626  
Phe Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp  
195 200 205

gag ttg tgg tcc ctg ggc aag ggc gtc gtg gtt cca act cgg ttt gga 674  
Glu Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly  
210 215 220

aac gca gat ggc gcg gcc tgc cac ttc ccc ttc atc ttc gag ggc cgc 722  
Asn Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg  
225 230 235

tcc tac tct gcc tgc acc acc gac ggt cgc tcc gac ggc ttg ccc tgg 770  
Ser Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp

240	245	250	255	
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Cys Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys				
	260	265	270	
ccc agc gag aga ctc tac acc cgg gac ggc aat gct gat ggg aaa ccc				866
Pro Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro				
	275	280	285	
tgc cag ttt cca ttc atc ttc caa ggc caa tcc tac tcc gcc tgc acc				914
Cys Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr				
	290	295	300	
acg gac ggt cgc tcc gac ggc tac cgc tgg tgc gcc acc acc gcc aac				962
Thr Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn				
	305	310	315	
tac gac cgg gac aag ctc ttc ggc ttc tgc ccg acc cga gct gac tcg				1010
Tyr Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser				
	320	325	330	335
acg gtg atg ggg ggc aac tcg gcg ggg gag ctg tgc gtc ttc ccc ttc				1058
Thr Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe				
	340	345	350	
act ttc ctg ggt aag gag tac tcg acc tgt acc agc gag ggc cgc gga				1106
Thr Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly				
	355	360	365	
gat ggg cgc ctc tgg tgc gct acc acc tcg aac ttt gac agc gac aag				1154
Asp Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys				
	370	375	380	
aag tgg ggc ttc tgc ccg gac caa gga tac agt ttg ttc ctc gtg gcg				1202
Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala				
	385	390	395	
gcg cat gag ttc ggc cac gcg ctg ggc tta gat cat tcc tca gtg ccg				1250
Ala His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro				
	400	405	410	415
gag gcg ctc atg tac cct atg tac cgc ttc act gag ggg ccc ccc ttg				1298
Glu Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu				
	420	425	430	
cat aag gac gac gtg aat ggc atc cgg cac ctc tat ggt cct cgc cct				1346
His Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro				
	435	440	445	
gaa cct gag cca cgg cct cca acc acc acc aca ccg cag ccc acg gct				1394
Glu Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala				
	450	455	460	
ccc ccg acg gtc tgc ccc acc gga ccc ccc act gtc cac ccc tca gag				1442
Pro Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu				
	465	470	475	
cgc ccc aca gct ggc ccc aca ggt ccc ccc tca gct ggc ccc aca ggt				1490
Arg Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly				
	480	485	490	495

ccc ccc act gct ggc cct tct acg gcc act act gtg cct ttg agt ccg 1538  
 Pro Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro  
 500 505 510

gtg gac gat gcc tgc aac gtg aac atc ttc gac gcc atc gcg gag att 1586  
 Val Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile  
 515 520 525

ggg aac cag ctg tat ttg ttc aag gat ggg aag tac tgg cga ttc tct 1634  
 Gly Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser  
 530 535 540

gag ggc agg ggg agc cgg ccg cag gcc ccc ttc ctt atc gcc gac aag 1682  
 Glu Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys  
 545 550 555

tgg ccc gcg ctg ccc cgc aag ctg gac tcg gtc ttt gag gag ccg ctc 1730  
 Trp Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu  
 560 565 570 575

tcc aag aag ctt ttc ttc ttc tct ggg cgc cag gtg tgg gtg tac aca 1778  
 Ser Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr  
 580 585 590

ggc gcg tcg gtg ctg ggc ccg agg cgt ctg gac aag ctg ggc ctg gga 1826  
 Gly Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly  
 595 600 605

gcc gac gtg gcc cag gtg acc ggg gcc ctc cgg agt gcc agg ggg aag 1874  
 Ala Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys  
 610 615 620

atg ctg ctg ttc agc ggg cgg cgc ctc tgg agg ttc gac gtg aag gcg 1922  
 Met Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala  
 625 630 635

cag atg gtg gat ccc cgg agc gcc agc gag gtg gac cgg atg ttc ccc 1970  
 Gln Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro  
 640 645 650 655

ggg gtg cct ttg gac acg cac gac gtc ttc cag tac cga gag aaa gcc 2018  
 Gly Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala  
 660 665 670

tat ttc tgc cag gac cgc ttc tac tgg cgc gtg agt tcc cgg agt gag 2066  
 Tyr Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu  
 675 680 685

ttg aac cag gtg gac caa gtg ggc tac gtg acc tat gac atc ctg cag 2114  
 Leu Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln  
 690 695 700

tgc cct gag gac tag ggctcccgtc ctgctttggc agtgccatgt aaatccccac 2169  
 Cys Pro Glu Asp \*  
 705

tgggaccaac cctggggaag gagccagttt gccggataca aactgggtatt ctgttctgga 2229  
 ggaaagggag gaggtaggt gggctgggcc ctctcttctc acctttgttt tttgttgagg 2289  
 tgtttctaataa aaacttgat tctctaacct ttataaaaaa aaaaaaaaaa aaaaaaaaaa 2349

2373

aaaaaaaaa aaaaaaaaaa aaaa

&lt;210&gt; 36

&lt;211&gt; 707

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 36

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Met Ser Leu Trp Gln Pro Leu Val Leu Val Leu Leu Val Leu Gly Cys
 1          5          10          15
Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe Pro
      20          25          30
Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
      35          40          45
Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser
      50          55          60
Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu
      65          70          75          80
Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr
      85          90          95
Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly
      100          105          110
Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr
      115          120          125
Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala
      130          135          140
Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr
      145          150          155          160
Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly
      165          170          175          180
Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe
      180          185          190
Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu
      195          200          205
Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn
      210          215          220
Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser
      225          230          235          240
Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys
      245          250          255
Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro
      260          265          270
Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys
      275          280          285
Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr
      290          295          300
Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr
      305          310          315          320
Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr
      325          330          335
Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr
      340          345          350
Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp
      355          360          365
Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys
      370          375          380
Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala
      385          390          395          400
His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu
      405          410          415
Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His

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420 425 430  
 Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu  
 435 440 445  
 Pro Glu Pro Arg Pro Pro Thr Thr Thr Pro Gln Pro Thr Ala Pro  
 450 455 460  
 Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg  
 465 470 475 480  
 Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro  
 485 490 495  
 Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val  
 500 505 510  
 Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly  
 515 520 525  
 Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu  
 530 535 540  
 Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp  
 545 550 555 560  
 Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser  
 565 570 575  
 Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly  
 580 585 590  
 Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala  
 595 600 605  
 Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met  
 610 615 620  
 Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln  
 625 630 635 640  
 Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly  
 645 650 655  
 Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr  
 660 665 670  
 Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu  
 675 680 685  
 Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln Cys  
 690 695 700  
 Pro Glu Asp  
 705

<210> 37  
 <211> 934  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (8)...(751)

<400> 37  
 tgagaag atg caa cca atc ctg ctt ctg ctg gcc ttc ctc ctg ctg ccc 49  
 Met Gln Pro Ile Leu Leu Leu Ala Phe Leu Leu Leu Pro  
 1 5 10  
 agg gca gat gca ggg gag atc atc ggg gga cat gag gcc aag ccc cac 97  
 Arg Ala Asp Ala Gly Glu Ile Ile Gly Gly His Glu Ala Lys Pro His  
 15 20 25 30  
 tcc cgc ccc tac atg gct tat ctt atg atc tgg gat cag aag tct ctg 145  
 Ser Arg Pro Tyr Met Ala Tyr Leu Met Ile Trp Asp Gln Lys Ser Leu  
 35 40 45



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aag agg tgc ggt ggc ttc ctg ata caa gac gac ttc gtg ctg aca gct 193
Lys Arg Cys Gly Gly Phe Leu Ile Gln Asp Asp Phe Val Leu Thr Ala
                    50                      55                      60

gct cac tgt tgg gga agc tcc ata aat gtc acc ttg ggg gcc cac aat 241
Ala His Cys Trp Gly Ser Ser Ile Asn Val Thr Leu Gly Ala His Asn
                    65                      70                      75

atc aaa gaa cag gag ccg acc cag cag ttt atc cct gtg aaa aga ccc 289
Ile Lys Glu Gln Glu Pro Thr Gln Gln Phe Ile Pro Val Lys Arg Pro
                    80                      85                      90

atc ccc cat cca gcc tat aat cct aag aac ttc tcc aac gac atc atg 337
Ile Pro His Pro Ala Tyr Asn Pro Lys Asn Phe Ser Asn Asp Ile Met
                    95                      100                      105                      110

cta ctg cag ctg gag aga aag gcc aag cgg acc aga gct gtg cag ccc 385
Leu Leu Gln Leu Glu Arg Lys Ala Lys Arg Thr Arg Ala Val Gln Pro
                    115                      120                      125

ctc agg cta cct agc aac aag gcc cag gtg aag cca ggg cag aca tgc 433
Leu Arg Leu Pro Ser Asn Lys Ala Gln Val Lys Pro Gly Gln Thr Cys
                    130                      135                      140

agt gtg gcc ggc tgg ggg cag acg gcc ccc ctg gga aaa cac tca cac 481
Ser Val Ala Gly Trp Gly Gln Thr Ala Pro Leu Gly Lys His Ser His
                    145                      150                      155

aca cta caa gag gtg aag atg aca gtg cag gaa gat cga aag tgc gaa 529
Thr Leu Gln Glu Val Lys Met Thr Val Gln Glu Asp Arg Lys Cys Glu
                    160                      165                      170

tct gac tta cgc cat tat tac gac agt acc att gag ttg tgc gtg ggg 577
Ser Asp Leu Arg His Tyr Tyr Asp Ser Thr Ile Glu Leu Cys Val Gly
                    175                      180                      185                      190

gac cca gag att aaa aag act tcc ttt aag ggg gac tct gga ggc cct 625
Asp Pro Glu Ile Lys Lys Thr Ser Phe Lys Gly Asp Ser Gly Gly Pro
                    195                      200                      205

ctt gtg tgt aac aag gtg gcc cag ggc att gtc tcc tat gga cga aac 673
Leu Val Cys Asn Lys Val Ala Gln Gly Ile Val Ser Tyr Gly Arg Asn
                    210                      215                      220

aat ggc atg cct cca cga gcc tgc acc aaa gtc tca agc ttt gta cac 721
Asn Gly Met Pro Pro Arg Ala Cys Thr Lys Val Ser Ser Phe Val His
                    225                      230                      235

tgg ata aag aaa acc atg aaa cgc tac taa ctacaggaag caaactaagc 771
Trp Ile Lys Lys Thr Met Lys Arg Tyr *
                    240                      245

ccccgctgta atgaaacacc ttctctggag ccaagtccag atttacctg ggagaggtgc 831
cagcaactga ataaatacct ctcccagtgt aaatctggag ccaagtccag atttacctg 891
ggagaggtgc cagcaactga ataaatacct ctagctgag tgg 934

<210> 38
<211> 247
<212> PRT
<213> Homo sapiens

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&lt;400&gt; 38

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Met Gln Pro Ile Leu Leu Leu Leu Ala Phe Leu Leu Leu Pro Arg Ala
 1           5           10           15
Asp Ala Gly Glu Ile Ile Gly Gly His Glu Ala Lys Pro His Ser Arg
          20           25           30
Pro Tyr Met Ala Tyr Leu Met Ile Trp Asp Gln Lys Ser Leu Lys Arg
      35           40           45
Cys Gly Gly Phe Leu Ile Gln Asp Asp Phe Val Leu Thr Ala Ala His
 50           55           60
Cys Trp Gly Ser Ser Ile Asn Val Thr Leu Gly Ala His Asn Ile Lys
 65           70           75           80
Glu Gln Glu Pro Thr Gln Gln Phe Ile Pro Val Lys Arg Pro Ile Pro
          85           90           95
His Pro Ala Tyr Asn Pro Lys Asn Phe Ser Asn Asp Ile Met Leu Leu
      100           105           110
Gln Leu Glu Arg Lys Ala Lys Arg Thr Arg Ala Val Gln Pro Leu Arg
      115           120           125
Leu Pro Ser Asn Lys Ala Gln Val Lys Pro Gly Gln Thr Cys Ser Val
      130           135           140
Ala Gly Trp Gly Gln Thr Ala Pro Leu Gly Lys His Ser His Thr Leu
 145           150           155           160
Gln Glu Val Lys Met Thr Val Gln Glu Asp Arg Lys Cys Glu Ser Asp
          165           170           175
Leu Arg His Tyr Tyr Asp Ser Thr Ile Glu Leu Cys Val Gly Asp Pro
      180           185           190
Glu Ile Lys Lys Thr Ser Phe Lys Gly Asp Ser Gly Gly Pro Leu Val
      195           200           205
Cys Asn Lys Val Ala Gln Gly Ile Val Ser Tyr Gly Arg Asn Asn Gly
      210           215           220
Met Pro Pro Arg Ala Cys Thr Lys Val Ser Ser Phe Val His Trp Ile
 225           230           235           240
Lys Lys Thr Met Lys Arg Tyr
          245

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&lt;210&gt; 39

&lt;211&gt; 1853

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (27)...(1814)

&lt;400&gt; 39

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aaaacgcagg gagggaggct gtcacc atg ccg gcc tgc tgc agc tgc agt gat 53
                               Met Pro Ala Cys Ser Cys Ser Asp
                               1           5

gtt ttc cag tat gag acg aac aaa gtc act cgg atc cag agc atg aat 101
Val Phe Gln Tyr Glu Thr Asn Lys Val Thr Arg Ile Gln Ser Met Asn
 10           15           20           25

tat ggc acc att aag tgg ttc ttc cac gtg atc atc ttt tcc tac gtt 149
Tyr Gly Thr Ile Lys Trp Phe Phe His Val Ile Ile Phe Ser Tyr Val
          30           35           40

tgc ttt gct ctg gtg agt gac aag ctg tac cag cgg aaa gag cct gtc 197
Cys Phe Ala Leu Val Ser Asp Lys Leu Tyr Gln Arg Lys Glu Pro Val
          45           50           55

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atc agt tct gtg cac acc aag gtg aag ggg ata gca gag gtg aaa gag	245
Ile Ser Ser Val His Thr Lys Val Lys Gly Ile Ala Glu Val Lys Glu	
60 65 70	
gag atc gtg gag aat gga gtg aag aag ttg gtg cac agt gtc ttt gag	293
Glu Ile Val Glu Asn Gly Val Lys Lys Leu Val His Ser Val Phe Asp	
75 80 85	
acc gca gac tac acc ttc cct ttg cag ggg aac tct ttc ttc gtg atg	341
Thr Ala Asp Tyr Thr Phe Pro Leu Gln Gly Asn Ser Phe Phe Val Met	
90 95 100 105	
aca aac ttt ctc aaa aca gaa ggc caa gag cag cgg ttg tgt ccc gag	389
Thr Asn Phe Leu Lys Thr Glu Gly Gln Glu Gln Arg Leu Cys Pro Glu	
110 115 120	
tat ccc acc cgc agg acg ctc tgt tcc tct gac cga ggt tgt aaa aag	437
Tyr Pro Thr Arg Arg Thr Leu Cys Ser Ser Asp Arg Gly Cys Lys Lys	
125 130 135	
gga tgg atg gac ccg cag agc aaa gga att cag acc gga agg tgt gta	485
Gly Trp Met Asp Pro Gln Ser Lys Gly Ile Gln Thr Gly Arg Cys Val	
140 145 150	
gtg cat gaa ggg aac cag aag acc tgt gaa gtc tct gcc tgg tgc ccc	533
Val His Glu Gly Asn Gln Lys Thr Cys Glu Val Ser Ala Trp Cys Pro	
155 160 165	
atc gag gca gtg gaa gag gcc ccc cgg cct gct ctc ttg aac agt gcc	581
Ile Glu Ala Val Glu Glu Ala Pro Arg Pro Ala Leu Leu Asn Ser Ala	
170 175 180 185	
gaa aac ttc act gtg ctc atc aag aac aat atc gac ttc ccc ggc cac	629
Glu Asn Phe Thr Val Leu Ile Lys Asn Asn Ile Asp Phe Pro Gly His	
190 195 200	
aac tac acc acg aga aac atc ctg cca ggt tta aac atc act tgt acc	677
Asn Tyr Thr Thr Arg Asn Ile Leu Pro Gly Leu Asn Ile Thr Cys Thr	
205 210 215	
ttc cac aag act cag aat cca cag tgt ccc att ttc cga cta gga gac	725
Phe His Lys Thr Gln Asn Pro Gln Cys Pro Ile Phe Arg Leu Gly Asp	
220 225 230	
atc ttc cga gaa aca ggc gat aat ttt tca gat gtg gca att cag ggc	773
Ile Phe Arg Glu Thr Gly Asp Asn Phe Ser Asp Val Ala Ile Gln Gly	
235 240 245	
gga ata atg ggc att gag atc tac tgg gac tgc aac cta gac cgt tgg	821
Gly Ile Met Gly Ile Glu Ile Tyr Trp Asp Cys Asn Leu Asp Arg Trp	
250 255 260 265	
ttc cat cac tgc cat ccc aaa tac agt ttc cgt cgc ctt gac gac aag	869
Phe His His Cys His Pro Lys Tyr Ser Phe Arg Arg Leu Asp Asp Lys	
270 275 280	
acc acc aac gtg tcc ttg tac cct ggc tac aac ttc aga tac gcc aag	917
Thr Thr Asn Val Ser Leu Tyr Pro Gly Tyr Asn Phe Arg Tyr Ala Lys	
285 290 295	
tac tac aag gaa aac aat gtt gag aaa cgg act ctg ata aaa gtc ttc	965

Tyr Tyr Lys Glu Asn Asn Val Glu Lys Arg Thr Leu Ile Lys Val Phe  
 300 305 310  
 ggg atc cgt ttt gac atc ctg gtt ttt ggc acc gga gga aaa ttt gac 1013  
 Gly Ile Arg Phe Asp Ile Leu Val Phe Gly Thr Gly Gly Lys Phe Asp  
 315 320 325  
 att atc cag ctg gtt gtg tac atc ggc tca acc ctc tcc tac ttc ggt 1061  
 Ile Ile Gln Leu Val Val Tyr Ile Gly Ser Thr Leu Ser Tyr Phe Gly  
 330 335 340 345  
 ctg gcc gct gtg ttc atc gac ttc ctc atc gac act tac tcc agt aac 1109  
 Leu Ala Ala Val Phe Ile Asp Phe Leu Ile Asp Thr Tyr Ser Ser Asn  
 350 355 360  
 tgc tgt cgc tcc cat att tat ccc tgg tgc aag tgc tgt cag ccc tgt 1157  
 Cys Cys Arg Ser His Ile Tyr Pro Trp Cys Lys Cys Cys Gln Pro Cys  
 365 370 375  
 gtg gtc aac gaa tac tac tac agg aag aag tgc gag tcc att gtg gag 1205  
 Val Val Asn Glu Tyr Tyr Tyr Arg Lys Lys Cys Glu Ser Ile Val Glu  
 380 385 390  
 cca aag ccg aca tta aag tat gtg tcc ttt gtg gat gaa tcc cac att 1253  
 Pro Lys Pro Thr Leu Lys Tyr Val Ser Phe Val Asp Glu Ser His Ile  
 395 400 405  
 agg atg gtg aac cag cag cta cta ggg aga agt ctg caa gat gtc aag 1301  
 Arg Met Val Asn Gln Gln Leu Leu Gly Arg Ser Leu Gln Asp Val Lys  
 410 415 420 425  
 ggc caa gaa gtc cca aga cct gcg atg gac ttc aca gat ttg tcc agg 1349  
 Gly Gln Glu Val Pro Arg Pro Ala Met Asp Phe Thr Asp Leu Ser Arg  
 430 435 440  
 ctg ccc ctg gcc ctc cat gac aca ccc ccg att cct gga caa cca gag 1397  
 Leu Pro Leu Ala Leu His Asp Thr Pro Pro Ile Pro Gly Gln Pro Glu  
 445 450 455  
 gag ata cag ctg ctt aga aag gag gcg act cct aga tcc agg gat agc 1445  
 Glu Ile Gln Leu Leu Arg Lys Glu Ala Thr Pro Arg Ser Arg Asp Ser  
 460 465 470  
 ccc gtc tgg tgc cag tgt gga agc tgc ctc cca tct caa ctc cct gag 1493  
 Pro Val Trp Cys Gln Cys Gly Ser Cys Leu Pro Ser Gln Leu Pro Glu  
 475 480 485  
 agc cac agg tgc ctg gag gag ctg tgc tgc cgg aaa aag ccg ggg gcc 1541  
 Ser His Arg Cys Leu Glu Glu Leu Cys Cys Arg Lys Lys Pro Gly Ala  
 490 495 500 505  
 tgc atc acc acc tca gag ctg ttc agg aag ctg gtc ctg tcc aga cac 1589  
 Cys Ile Thr Thr Ser Glu Leu Phe Arg Lys Leu Val Leu Ser Arg His  
 510 515 520  
 gtc ctg cag ttc ctc ctg ctc tac cag gag ccc ttg ctg gcg ctg gat 1637  
 Val Leu Gln Phe Leu Leu Leu Tyr Gln Glu Pro Leu Leu Ala Leu Asp  
 525 530 535  
 gtg gat tcc acc aac agc cgg ctg cgg cac tgt gcc tac agg tgc tac 1685  
 Val Asp Ser Thr Asn Ser Arg Leu Arg His Cys Ala Tyr Arg Cys Tyr

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      540              545              550
gcc acc tgg cgc ttc ggc tcc cag gac atg gct gac ttt gcc atc ctg 1733
Ala Thr Trp Arg Phe Gly Ser Gln Asp Met Ala Asp Phe Ala Ile Leu
    555              560              565

ccc agc tgc tgc cgc tgg agg atc cgg aaa gag ttt ccg aag agt gaa 1781
Pro Ser Cys Cys Arg Trp Arg Ile Arg Lys Glu Phe Pro Lys Ser Glu
    570              575              580              585

ggg cag tac agt ggc ttc aag agt cct tac tga agccaggcac cgtggctcac 1834
Gly Gln Tyr Ser Gly Phe Lys Ser Pro Tyr *
    590              595

gtctgtaatc ccacctttt 1853

<210> 40
<211> 595
<212> PRT
<213> Homo sapiens

<400> 40
Met Pro Ala Cys Cys Ser Cys Ser Asp Val Phe Gln Tyr Glu Thr Asn
  1          5          10          15
Lys Val Thr Arg Ile Gln Ser Met Asn Tyr Gly Thr Ile Lys Trp Phe
    20          25          30
Phe His Val Ile Ile Phe Ser Tyr Val Cys Phe Ala Leu Val Ser Asp
    35          40          45
Lys Leu Tyr Gln Arg Lys Glu Pro Val Ile Ser Ser Val His Thr Lys
    50          55          60
Val Lys Gly Ile Ala Glu Val Lys Glu Glu Ile Val Glu Asn Gly Val
    65          70          75          80
Lys Lys Leu Val His Ser Val Phe Asp Thr Ala Asp Tyr Thr Phe Pro
    85          90          95
Leu Gln Gly Asn Ser Phe Phe Val Met Thr Asn Phe Leu Lys Thr Glu
    100          105          110
Gly Gln Glu Gln Arg Leu Cys Pro Glu Tyr Pro Thr Arg Arg Thr Leu
    115          120          125
Cys Ser Ser Asp Arg Gly Cys Lys Lys Gly Trp Met Asp Pro Gln Ser
    130          135          140
Lys Gly Ile Gln Thr Gly Arg Cys Val Val His Glu Gly Asn Gln Lys
    145          150          155          160
Thr Cys Glu Val Ser Ala Trp Cys Pro Ile Glu Ala Val Glu Glu Ala
    165          170          175
Pro Arg Pro Ala Leu Leu Asn Ser Ala Glu Asn Phe Thr Val Leu Ile
    180          185          190
Lys Asn Asn Ile Asp Phe Pro Gly His Asn Tyr Thr Thr Arg Asn Ile
    195          200          205
Leu Pro Gly Leu Asn Ile Thr Cys Thr Phe His Lys Thr Gln Asn Pro
    210          215          220
Gln Cys Pro Ile Phe Arg Leu Gly Asp Ile Phe Arg Glu Thr Gly Asp
    225          230          235          240
Asn Phe Ser Asp Val Ala Ile Gln Gly Gly Ile Met Gly Ile Glu Ile
    245          250          255
Tyr Trp Asp Cys Asn Leu Asp Arg Trp Phe His His Cys His Pro Lys
    260          265          270
Tyr Ser Phe Arg Arg Leu Asp Asp Lys Thr Thr Asn Val Ser Leu Tyr
    275          280          285
Pro Gly Tyr Asn Phe Arg Tyr Ala Lys Tyr Tyr Lys Glu Asn Asn Val
    290          295          300
Glu Lys Arg Thr Leu Ile Lys Val Phe Gly Ile Arg Phe Asp Ile Leu

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<210> 41
<211> 1700
<212> DNA
<213> Homo sapiens
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<220>
<221> CDS
<222> (125)...(1585)
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<400> 41
cggaattggt gggttcttgg tctcactgag ttctagaatg aagctgcaga ccctcgcast 60
gagtgttaca gctcttaagg ctctctgact gccacccctg cctgcctgcc cggccctgca 120
caac atg cag ccc tcc ggc ctc gag ggt ccc ggc acg ttt ggt cgg tgg 169
Met Gln Pro Ser Gly Leu Glu Gly Pro Gly Thr Phe Gly Arg Trp
1 5 10 15
cct ctg ctg agt ctg ctg ctc ctg ctg ctg ctg ctc cag cct gta acc 217
Pro Leu Leu Ser Leu Leu Leu Leu Leu Leu Leu Leu Gln Pro Val Thr
20 25 30
tgt gcc tac acc acg cca ggc ccc ccc aga gcc ctc acc acg ctg ggc 265

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Cys	Ala	Tyr	Thr	Thr	Pro	Gly	Pro	Pro	Arg	Ala	Leu	Thr	Thr	Leu	Gly		
			35					40					45				
gcc	ccc	aga	gcc	cac	acc	atg	ccg	ggc	acc	tac	gct	ccc	tcg	acc	aca	313	
Ala	Pro	Arg	Ala	His	Thr	Met	Pro	Gly	Thr	Tyr	Ala	Pro	Ser	Thr	Thr		
			50				55					60					
ctc	agt	agt	ccc	agc	acc	cag	ggc	ctg	caa	gag	cag	gca	cgg	gcc	ctg	361	
Leu	Ser	Ser	Pro	Ser	Thr	Gln	Gly	Leu	Gln	Glu	Gln	Ala	Arg	Ala	Leu		
			65			70					75						
atg	cgg	gac	ttc	ccg	ctc	gtg	gac	ggc	cac	aac	gac	ctg	ccc	ctg	gtc	409	
Met	Arg	Asp	Phe	Pro	Leu	Val	Asp	Gly	His	Asn	Asp	Leu	Pro	Leu	Val		
			80			85				90					95		
cta	agg	cag	gtt	tac	cag	aaa	ggg	cta	cag	gat	gtt	aac	ctg	cgc	aat	457	
Leu	Arg	Gln	Val	Tyr	Gln	Lys	Gly	Leu	Gln	Asp	Val	Asn	Leu	Arg	Asn		
				100					105					110			
ttc	agc	tac	ggc	cag	acc	agc	ctg	gac	agg	ctt	aga	gat	ggc	ctc	gtg	505	
Phe	Ser	Tyr	Gly	Gln	Thr	Ser	Leu	Asp	Arg	Leu	Arg	Asp	Gly	Leu	Val		
			115					120					125				
ggc	gcc	cag	ttc	tgg	tca	gcc	tat	gtg	cca	tgc	cag	acc	cag	gac	cgg	553	
Gly	Ala	Gln	Phe	Trp	Ser	Ala	Tyr	Val	Pro	Cys	Gln	Thr	Gln	Asp	Arg		
			130				135					140					
gat	gcc	ctg	cgc	ctc	acc	ctg	gag	cag	att	gac	ctc	ata	cgc	cgc	atg	601	
Asp	Ala	Leu	Arg	Leu	Thr	Leu	Glu	Gln	Ile	Asp	Leu	Ile	Arg	Arg	Met		
			145			150					155						
tgt	gcc	tcc	tat	tct	gag	ctg	gag	ctt	gtg	acc	tcg	gct	aaa	gct	ctg	649	
Cys	Ala	Ser	Tyr	Ser	Glu	Leu	Glu	Leu	Val	Thr	Ser	Ala	Lys	Ala	Leu		
					165					170				175			
aac	gac	act	cag	aaa	ttg	gcc	tgc	ctc	atc	ggg	gta	gag	ggg	ggc	cac	697	
Asn	Asp	Thr	Gln	Lys	Leu	Ala	Cys	Leu	Ile	Gly	Val	Glu	Gly	Gly	His		
				180					185					190			
tcg	ctg	gac	aat	agc	ctc	tcc	atc	tta	cgt	acc	ttc	tac	atg	ctg	gga	745	
Ser	Leu	Asp	Asn	Ser	Leu	Ser	Ile	Leu	Arg	Thr	Phe	Tyr	Met	Leu	Gly		
			195				200						205				
gtg	cgc	tac	ctg	acg	ctc	acc	cac	acc	tgc	aac	aca	ccc	tgg	gca	gag	793	
Val	Arg	Tyr	Leu	Thr	Leu	Thr	His	Thr	Cys	Asn	Thr	Pro	Trp	Ala	Glu		
			210				215					220					
agc	tcc	gct	aag	ggc	gtc	cac	tcc	ttc	tac	aac	aac	atc	agc	ggg	ctg	841	
Ser	Ser	Ala	Lys	Gly	Val	His	Ser	Phe	Tyr	Asn	Asn	Ile	Ser	Gly	Leu		
			225			230					235						
act	gac	ttt	ggg	gag	aag	gtg	gtg	gca	gaa	atg	aac	cgc	ctg	ggc	atg	889	
Thr	Asp	Phe	Gly	Glu	Lys	Val	Val	Ala	Glu	Met	Asn	Arg	Leu	Gly	Met		
					245				250					255			
atg	gta	gac	tta	tcc	cat	gtc	tca	gat	gct	gtg	gca	cgg	cgg	gcc	ctg	937	
Met	Val	Asp	Leu	Ser	His	Val	Ser	Asp	Ala	Val	Ala	Arg	Arg	Ala	Leu		
				260				265						270			
gaa	gtg	tca	cag	gca	cct	gtg	atc	ttc	tcc	cac	tcg	gct	gcc	cgg	ggg	985	
Glu	Val	Ser	Gln	Ala	Pro	Val	Ile	Phe	Ser	His	Ser	Ala	Ala	Arg	Gly		

275	280	285	
gtg tgc aac agt gct cgg aat gtt cct gat gac atc ctg cag ctt ctg			1033
Val Cys Asn Ser Ala Arg Asn Val Pro Asp Asp Ile Leu Gln Leu Leu			
290	295	300	
aag aag aac ggt ggc gtc gtg atg gtg tct ttg tcc atg gga gta ata			1081
Lys Lys Asn Gly Gly Val Val Met Val Ser Leu Ser Met Gly Val Ile			
305	310	315	
cag tgc aac cca tca gcc aat gtg tcc act gtg gca gat cac ttc gac			1129
Gln Cys Asn Pro Ser Ala Asn Val Ser Thr Val Ala Asp His Phe Asp			
320	325	330	335
cac atc aag gct gtc att gga tcc aag ttc atc ggg att ggt gga gat			1177
His Ile Lys Ala Val Ile Gly Ser Lys Phe Ile Gly Ile Gly Gly Asp			
340	345		350
tat gat ggg gcc ggc aaa ttc cct cag ggg ctg gaa gac gtg tcc aca			1225
Tyr Asp Gly Ala Gly Lys Phe Pro Gln Gly Leu Glu Asp Val Ser Thr			
355	360		365
tac ccg gtc ctg ata gag gag ttg ctg agt cgt ggc tgg agt gag gaa			1273
Tyr Pro Val Leu Ile Glu Glu Leu Leu Ser Arg Gly Trp Ser Glu Glu			
370	375		380
gag ctt cag ggt gtc ctt cgt gga aac ctg ctg cgg gtc ttc aga caa			1321
Glu Leu Gln Gly Val Leu Arg Gly Asn Leu Leu Arg Val Phe Arg Gln			
385	390		395
gtg gaa aag gta cag gaa gaa aac aaa tgg caa agc ccc ttg gag gac			1369
Val Glu Lys Val Gln Glu Glu Asn Lys Trp Gln Ser Pro Leu Glu Asp			
400	405	410	415
aag ttc ccg gat gag cag ctg agc agt tcc tgc cac tcc gac ctc tca			1417
Lys Phe Pro Asp Glu Gln Leu Ser Ser Ser Cys His Ser Asp Leu Ser			
420	425		430
cgt ctg cgt cag aga cag agt ctg act tca ggc cag gaa ctc act gag			1465
Arg Leu Arg Gln Arg Gln Ser Leu Thr Ser Gly Gln Glu Leu Thr Glu			
435	440		445
att ccc ata cac tgg aca gcc aag tta cca gcc aag tgg tca gtc tca			1513
Ile Pro Ile His Trp Thr Ala Lys Leu Pro Ala Lys Trp Ser Val Ser			
450	455		460
gag tcc tcc ccc cac atg gcc cca gtc ctt gca gtt gtg gcc acc ttc			1561
Glu Ser Ser Pro His Met Ala Pro Val Leu Ala Val Val Ala Thr Phe			
465	470	475	
cca gtc ctt att ctg tgg ctc tga tgaccagtt agtcctgcca gatgtcactg			1615
Pro Val Leu Ile Leu Trp Leu *			
480	485		
tagcaagcca cagacacccc acaaagttcc cctgttgtgc aggcacaaat atttcttgaa			1675
ataaatgtttt tggacataga aaaaa			1700

&lt;210&gt; 42

&lt;211&gt; 486

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens



&lt;400&gt; 42

Met Gln Pro Ser Gly Leu Glu Gly Pro Gly Thr Phe Gly Arg Trp Pro  
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 Leu Leu Ser Leu Leu Leu Leu Leu Leu Gln Pro Val Thr Cys  
 20 25 30  
 Ala Tyr Thr Thr Pro Gly Pro Pro Arg Ala Leu Thr Thr Leu Gly Ala  
 35 40 45  
 Pro Arg Ala His Thr Met Pro Gly Thr Tyr Ala Pro Ser Thr Thr Leu  
 50 55 60  
 Ser Ser Pro Ser Thr Gln Gly Leu Gln Glu Gln Ala Arg Ala Leu Met  
 65 70 75 80  
 Arg Asp Phe Pro Leu Val Asp Gly His Asn Asp Leu Pro Leu Val Leu  
 85 90 95  
 Arg Gln Val Tyr Gln Lys Gly Leu Gln Asp Val Asn Leu Arg Asn Phe  
 100 105 110  
 Ser Tyr Gly Gln Thr Ser Leu Asp Arg Leu Arg Asp Gly Leu Val Gly  
 115 120 125  
 Ala Gln Phe Trp Ser Ala Tyr Val Pro Cys Gln Thr Gln Asp Arg Asp  
 130 135 140  
 Ala Leu Arg Leu Thr Leu Glu Gln Ile Asp Leu Ile Arg Arg Met Cys  
 145 150 155 160  
 Ala Ser Tyr Ser Glu Leu Glu Leu Val Thr Ser Ala Lys Ala Leu Asn  
 165 170 175  
 Asp Thr Gln Lys Leu Ala Cys Leu Ile Gly Val Glu Gly Gly His Ser  
 180 185 190  
 Leu Asp Asn Ser Leu Ser Ile Leu Arg Thr Phe Tyr Met Leu Gly Val  
 195 200 205  
 Arg Tyr Leu Thr Leu Thr His Thr Cys Asn Thr Pro Trp Ala Glu Ser  
 210 215 220  
 Ser Ala Lys Gly Val His Ser Phe Tyr Asn Asn Ile Ser Gly Leu Thr  
 225 230 235 240  
 Asp Phe Gly Glu Lys Val Val Ala Glu Met Asn Arg Leu Gly Met Met  
 245 250 255  
 Val Asp Leu Ser His Val Ser Asp Ala Val Ala Arg Arg Ala Leu Glu  
 260 265 270  
 Val Ser Gln Ala Pro Val Ile Phe Ser His Ser Ala Ala Arg Gly Val  
 275 280 285  
 Cys Asn Ser Ala Arg Asn Val Pro Asp Asp Ile Leu Gln Leu Leu Lys  
 290 295 300  
 Lys Asn Gly Gly Val Val Met Val Ser Leu Ser Met Gly Val Ile Gln  
 305 310 315 320  
 Cys Asn Pro Ser Ala Asn Val Ser Thr Val Ala Asp His Phe Asp His  
 325 330 335  
 Ile Lys Ala Val Ile Gly Ser Lys Phe Ile Gly Ile Gly Gly Asp Tyr  
 340 345 350  
 Asp Gly Ala Gly Lys Phe Pro Gln Gly Leu Glu Asp Val Ser Thr Tyr  
 355 360 365  
 Pro Val Leu Ile Glu Glu Leu Leu Ser Arg Gly Trp Ser Glu Glu Glu  
 370 375 380  
 Leu Gln Gly Val Leu Arg Gly Asn Leu Leu Arg Val Phe Arg Gln Val  
 385 390 395 400  
 Glu Lys Val Gln Glu Glu Asn Lys Trp Gln Ser Pro Leu Glu Asp Lys  
 405 410 415  
 Phe Pro Asp Glu Gln Leu Ser Ser Ser Cys His Ser Asp Leu Ser Arg  
 420 425 430  
 Leu Arg Gln Arg Gln Ser Leu Thr Ser Gly Gln Glu Leu Thr Glu Ile  
 435 440 445  
 Pro Ile His Trp Thr Ala Lys Leu Pro Ala Lys Trp Ser Val Ser Glu  
 450 455 460  
 Ser Ser Pro His Met Ala Pro Val Leu Ala Val Val Ala Thr Phe Pro

465 470 475 480  
Val Leu Ile Leu Trp Leu  
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<212> DNA  
<213> Homo sapiens

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<222> (81)...(1826)

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tggctgcagt tggcgggccc atg tgg ggg cgc acg gcg cgg cgc tgc ccg 113  
Met Trp Gly Arg Thr Ala Arg Arg Arg Cys Pro  
1 5 10

cgg gaa ctg cgg cgc ggc cgg gag gcg ctg ttg gtg ctc ctg gcg cta 161  
Arg Glu Leu Arg Arg Gly Arg Glu Ala Leu Leu Val Leu Leu Ala Leu  
15 20 25

ctg gcg ttg gcc ggg ctg ggc tgc gtg ctg cgg gcg cag cgt ggg gcc 209  
Leu Ala Leu Ala Gly Leu Gly Ser Val Leu Arg Ala Gln Arg Gly Ala  
30 35 40

ggg gcc ggg gct gcc gag ccg gga ccc ccg cgc acc ccg cgc ccc ggg 257  
Gly Ala Gly Ala Ala Glu Pro Gly Pro Pro Arg Thr Pro Arg Pro Gly  
45 50 55

cgg cgc gag ccg gtc atg ccg cgg ccg ccg gtg ccg gcg aac gcg ctg 305  
Arg Arg Glu Pro Val Met Pro Arg Pro Pro Val Pro Ala Asn Ala Leu  
60 65 70 75

ggc gcg cgg ggc gag gcg gtg cgg ctg cag ctg cag ggc gag gag ctg 353  
Gly Ala Arg Gly Glu Ala Val Arg Leu Gln Leu Gln Gly Glu Glu Leu  
80 85 90

cgg ctg cag gag gag agc gtg cgg ctg cac cag att aac atc tac ctc 401  
Arg Leu Gln Glu Glu Ser Val Arg Leu His Gln Ile Asn Ile Tyr Leu  
95 100 105

agc gac cgc atc tca ctg cac cgc cgc ctg ccc gag cgc tgg aac ccg 449  
Ser Asp Arg Ile Ser Leu His Arg Arg Leu Pro Glu Arg Trp Asn Pro  
110 115 120

ctg tgc aaa gag aag aaa tat gat tat gat aat ttg ccc agg aca tct 497  
Leu Cys Lys Glu Lys Lys Tyr Asp Tyr Asp Asn Leu Pro Arg Thr Ser  
125 130 135

gtt atc ata gca ttt tat aat gaa gcc tgg tca act ctc ctt cgg aca 545  
Val Ile Ile Ala Phe Tyr Asn Glu Ala Trp Ser Thr Leu Leu Arg Thr  
140 145 150 155

gtt tac agt gtc ctt gag aca tcc ccg gat atc ctg cta gaa gaa gtg 593  
Val Tyr Ser Val Leu Glu Thr Ser Pro Asp Ile Leu Leu Glu Val  
160 165 170

atc ctt gta gat gac tac agt gat aga gag cac ctg aag gag cgc ttg Ile Leu Val Asp Asp Tyr Ser Asp Arg Glu His Leu Lys Glu Arg Leu 175 180 185	641
gcc aat gag ctt tcg gga ctg ccc aag gtg cgc ctg atc cgc gcc aac Ala Asn Glu Leu Ser Gly Leu Pro Lys Val Arg Leu Ile Arg Ala Asn 190 195 200	689
aag aga gag ggc ctg gtg cga gcc cgg ctg ctg ggg gcg tct gcg gcg Lys Arg Glu Gly Leu Val Arg Ala Arg Leu Leu Gly Ala Ser Ala Ala 205 210 215	737
agg ggc gat gtt ctg acc ttc ctg gac tgt cac tgt gag tgc cac gaa Arg Gly Asp Val Leu Thr Phe Leu Asp Cys His Cys Glu Cys His Glu 220 225 230 235	785
ggg tgg ctg gag ccg ctg ctg cag agg atc cat gaa gag gag tcg gca Gly Trp Leu Glu Pro Leu Leu Gln Arg Ile His Glu Glu Glu Ser Ala 240 245 250	833
gtg gtg tgc ccg gtg att gat gtg atc gac tgg aac acc ttc gaa tac Val Val Cys Pro Val Ile Asp Val Ile Asp Trp Asn Thr Phe Glu Tyr 255 260 265	881
ctg ggg aac tcc ggg gag ccc cag atc ggc ggt ttc gac tgg agg ctg Leu Gly Asn Ser Gly Glu Pro Gln Ile Gly Gly Phe Asp Trp Arg Leu 270 275 280	929
gtg ttc acg tgg cac aca gtt cct gag agg gag agg ata cgg atg caa Val Phe Thr Trp His Thr Val Pro Glu Arg Glu Arg Ile Arg Met Gln 285 290 295	977
tcc ccc gtc gat gtc atc agg tct cca aca atg gct ggt ggg ctg ttt Ser Pro Val Asp Val Ile Arg Ser Pro Thr Met Ala Gly Gly Leu Phe 300 305 310 315	1025
gct gtg agt aag aaa tat ttt gaa tat ctg ggg tct tat gat aca gga Ala Val Ser Lys Lys Tyr Phe Glu Tyr Leu Gly Ser Tyr Asp Thr Gly 320 325 330	1073
atg gaa gtt tgg gga gga gaa aac ctc gaa ttt tcc ttt agg atc tgg Met Glu Val Trp Gly Gly Glu Asn Leu Glu Phe Ser Phe Arg Ile Trp 335 340 345	1121
cag tgt ggt ggg gtt ctg gaa aca cac cca tgt tcc cat gtt ggc cat Gln Cys Gly Gly Val Leu Glu Thr His Pro Cys Ser His Val Gly His 350 355 360	1169
gtt ttc ccc aag caa gct ccc tac tcc cgc aac aag gct ctg gcc aac Val Phe Pro Lys Gln Ala Pro Tyr Ser Arg Asn Lys Ala Leu Ala Asn 365 370 375	1217
agt gtt cgt gca gct gaa gta tgg atg gat gaa ttt aaa gag ctc tac Ser Val Arg Ala Ala Glu Val Trp Met Asp Glu Phe Lys Glu Leu Tyr 380 385 390 395	1265
tac cat cgc aac ccc cgt gcc cgc ttg gaa cct ttt ggg gat gtg aca Tyr His Arg Asn Pro Arg Ala Arg Leu Glu Pro Phe Gly Asp Val Thr 400 405 410	1313
gag agg aag cag ctc cgg gac aag ctc cag tgt aaa gac ttc aag tgg	1361

Glu Arg Lys Gln Leu Arg Asp Lys Leu Gln Cys Lys Asp Phe Lys Trp  
 415 420 425  
 ttc ttg gag act gtg tat cca gaa ctg cat gtg cct gag gac agg cct 1409  
 Phe Leu Glu Thr Val Tyr Pro Glu Leu His Val Pro Glu Asp Arg Pro  
 430 435 440  
 ggc ttc ttc ggg atg ctc cag aac aaa gga cta aca gac tac tgc ttt 1457  
 Gly Phe Phe Gly Met Leu Gln Asn Lys Gly Leu Thr Asp Tyr Cys Phe  
 445 450 455  
 gac tat aac cct ccc gat gaa aac cag att gtg gga cac cag gtc att 1505  
 Asp Tyr Asn Pro Pro Asp Glu Asn Gln Ile Val Gly His Gln Val Ile  
 460 465 470 475  
 ctg tac ctc tgt cat ggg atg ggc cag aat cag ttt ttc gag tac acg 1553  
 Leu Tyr Leu Cys His Gly Met Gly Gln Asn Gln Phe Phe Glu Tyr Thr  
 480 485 490  
 tcc cag aaa gaa ata cgc tat aac acc cac cag cct gag ggc tgc att 1601  
 Ser Gln Lys Glu Ile Arg Tyr Asn Thr His Gln Pro Glu Gly Cys Ile  
 495 500 505  
 gct gtg gaa gca gga atg gat acc ctt atc atg cat ctc tgc gaa gaa 1649  
 Ala Val Glu Ala Gly Met Asp Thr Leu Ile Met His Leu Cys Glu Glu  
 510 515 520  
 act gcc cca gag aat cag aag ttc atc ttg cag gag gat gga tct tta 1697  
 Thr Ala Pro Glu Asn Gln Lys Phe Ile Leu Gln Glu Asp Gly Ser Leu  
 525 530 535  
 ttt cac gaa cag tcc aag aaa tgt gtc cag gct gcg agg aag gag tcg 1745  
 Phe His Glu Gln Ser Lys Lys Cys Val Gln Ala Ala Arg Lys Glu Ser  
 540 545 550 555  
 agt gac agt ttc gtt cca ctc tta cga gac tgc acc aac tcg gat cat 1793  
 Ser Asp Ser Phe Val Pro Leu Leu Arg Asp Cys Thr Asn Ser Asp His  
 560 565 570  
 cag aaa tgg ttc ttc aaa gag cgc atg tta tga agcctcgtgt atcaaggagc 1846  
 Gln Lys Trp Phe Phe Lys Glu Arg Met Leu \*  
 575 580  
 ccatacgaagg agactgtgga gccaggactc tgcccaacaa agacttagct aagcagtgac 1906  
 cagaacccac caaaaactag gctgcattgc tttgaagagg caatcatttt gccatttgtg 1966  
 aaagtgtgtg tggatttagt aaaaatgtga ataagctttg tacttatttt gagaactttt 2026  
 taaatgttcc aaaataccct attttcaaag ggtaatcgta agatgttaac ccttggtatt 2086  
 tagaaaaatta aaaccttata atatttttct atcaarawrw awattttaca gtcgtgcctt 2146  
 ttactctcat tagcaaaaaa gataaagatt ttattttggt atttacaaga attcccaggt 2206  
 acgaagatat ctgcatgggt ggaaatcagg ttcaagcaac gtactttgca ttaactgata 2266  
 atacctcagc tgcgggggta aagttttccc agtatagaga gactgtcact aggaacattg 2326  
 tattgattta ttcaggatcat tgagatcttc tagatgtatt ttaaaaagaa tgcttttttg 2386  
 ttatgtgttg ctaccacagt taacactcca taatgttcat gtcagccaaa gaggactaac 2446  
 caaagctgaa atctcagaga acaatttgct ttactaagct gagtcaactt gagagcgaac 2506  
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 atatcatttt taatttttat gatacggtag tgtcaggag aatgtaatg ttctatatga 2626  
 aattcctttt tcaagtttgt tcattaataa cagttattaa tttaaatacag cgtttagagt 2686  
 tgtgtgtgtg caactgtgtg gaaaatttct ctgagtaatt ctgatttgtg aatgatccca 2746  
 gaccaaccct gagattttgt caacctgatt aagtcaatat gaatgattaa aaagatgtga 2806  
 gaacaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 2850

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 <211> 581  
 <212> PRT  
 <213> Homo sapiens

<400> 44  
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 Leu Gly Ser Val Leu Arg Ala Gln Arg Gly Ala Gly Ala Gly Ala Ala  
 35 40 45  
 Glu Pro Gly Pro Pro Arg Thr Pro Arg Pro Gly Arg Arg Glu Pro Val  
 50 55 60  
 Met Pro Arg Pro Pro Val Pro Ala Asn Ala Leu Gly Ala Arg Gly Glu  
 65 70 75 80  
 Ala Val Arg Leu Gln Leu Gln Gly Glu Glu Leu Arg Leu Gln Glu Glu  
 85 90 95  
 Ser Val Arg Leu His Gln Ile Asn Ile Tyr Leu Ser Asp Arg Ile Ser  
 100 105 110  
 Leu His Arg Arg Leu Pro Glu Arg Trp Asn Pro Leu Cys Lys Glu Lys  
 115 120 125  
 Lys Tyr Asp Tyr Asp Asn Leu Pro Arg Thr Ser Val Ile Ile Ala Phe  
 130 135 140  
 Tyr Asn Glu Ala Trp Ser Thr Leu Leu Arg Thr Val Tyr Ser Val Leu  
 145 150 155 160  
 Glu Thr Ser Pro Asp Ile Leu Leu Glu Glu Val Ile Leu Val Asp Asp  
 165 170 175  
 Tyr Ser Asp Arg Glu His Leu Lys Glu Arg Leu Ala Asn Glu Leu Ser  
 180 185 190  
 Gly Leu Pro Lys Val Arg Leu Ile Arg Ala Asn Lys Arg Glu Gly Leu  
 195 200 205  
 Val Arg Ala Arg Leu Leu Gly Ala Ser Ala Ala Arg Gly Asp Val Leu  
 210 215 220  
 Thr Phe Leu Asp Cys His Cys Glu Cys His Glu Gly Trp Leu Glu Pro  
 225 230 235 240  
 Leu Leu Gln Arg Ile His Glu Glu Glu Ser Ala Val Val Cys Pro Val  
 245 250 255  
 Ile Asp Val Ile Asp Trp Asn Thr Phe Glu Tyr Leu Gly Asn Ser Gly  
 260 265 270  
 Glu Pro Gln Ile Gly Gly Phe Asp Trp Arg Leu Val Phe Thr Trp His  
 275 280 285  
 Thr Val Pro Glu Arg Glu Arg Ile Arg Met Gln Ser Pro Val Asp Val  
 290 295 300  
 Ile Arg Ser Pro Thr Met Ala Gly Gly Leu Phe Ala Val Ser Lys Lys  
 305 310 315 320  
 Tyr Phe Glu Tyr Leu Gly Ser Tyr Asp Thr Gly Met Glu Val Trp Gly  
 325 330 335  
 Gly Glu Asn Leu Glu Phe Ser Phe Arg Ile Trp Gln Cys Gly Gly Val  
 340 345 350  
 Leu Glu Thr His Pro Cys Ser His Val Gly His Val Phe Pro Lys Gln  
 355 360 365  
 Ala Pro Tyr Ser Arg Asn Lys Ala Leu Ala Asn Ser Val Arg Ala Ala  
 370 375 380  
 Glu Val Trp Met Asp Glu Phe Lys Glu Leu Tyr Tyr His Arg Asn Pro  
 385 390 395 400  
 Arg Ala Arg Leu Glu Pro Phe Gly Asp Val Thr Glu Arg Lys Gln Leu  
 405 410 415  
 Arg Asp Lys Leu Gln Cys Lys Asp Phe Lys Trp Phe Leu Glu Thr Val  
 420 425 430  
 Tyr Pro Glu Leu His Val Pro Glu Asp Arg Pro Gly Phe Phe Gly Met

435 440 445  
 Leu Gln Asn Lys Gly Leu Thr Asp Tyr Cys Phe Asp Tyr Asn Pro Pro  
 450 455 460  
 Asp Glu Asn Gln Ile Val Gly His Gln Val Ile Leu Tyr Leu Cys His  
 465 470 475 480  
 Gly Met Gly Gln Asn Gln Phe Phe Glu Tyr Thr Ser Gln Lys Glu Ile  
 485 490 495  
 Arg Tyr Asn Thr His Gln Pro Glu Gly Cys Ile Ala Val Glu Ala Gly  
 500 505 510  
 Met Asp Thr Leu Ile Met His Leu Cys Glu Glu Thr Ala Pro Glu Asn  
 515 520 525  
 Gln Lys Phe Ile Leu Gln Glu Asp Gly Ser Leu Phe His Glu Gln Ser  
 530 535 540  
 Lys Lys Cys Val Gln Ala Ala Arg Lys Glu Ser Ser Asp Ser Phe Val  
 545 550 555 560  
 Pro Leu Leu Arg Asp Cys Thr Asn Ser Asp His Gln Lys Trp Phe Phe  
 565 570 575  
 Lys Glu Arg Met Leu  
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<210> 45  
 <211> 2890  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (229)...(1116)

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 aggaatctgt gagccattgt caaaacgtcc attttcatct ggctgtgaaa gtgaggacca 180  
 caacaggtag gtattggttag aaacaggagt cctcagagaa gccccaag atg cag cct 237  
 Met Gln Pro  
 1  
 gag gga gca gaa aag gga aaa agc ttc aag cag aga ctg gtc ttg aag 285  
 Glu Gly Ala Glu Lys Gly Lys Ser Phe Lys Gln Arg Leu Val Leu Lys  
 5 10 15  
 agc agc tta gcg aaa gaa acc ctc tct gag ttc ttg ggc acg ttc atc 333  
 Ser Ser Leu Ala Lys Glu Thr Leu Ser Glu Phe Leu Gly Thr Phe Ile  
 20 25 30 35  
 ttg att gtc ctt gga tgt ggc tgt gtt gcc caa gct att ctc agt cga 381  
 Leu Ile Val Leu Gly Cys Gly Cys Val Ala Gln Ala Ile Leu Ser Arg  
 40 45 50  
 gga cgt ttt gga ggg gtc atc act atc aat gtt gga ttt tca atg gca 429  
 Gly Arg Phe Gly Gly Val Ile Thr Ile Asn Val Gly Phe Ser Met Ala  
 55 60 65  
 gtt gca atg gcc att tat gtg gct ggc ggt gtc tct ggt ggt cac atc 477  
 Val Ala Met Ala Ile Tyr Val Ala Gly Gly Val Ser Gly Gly His Ile  
 70 75 80  
 aac cca gct gtg tct tta gca atg tgt ctc ttt gga cgg atg aaa tgg 525  
 Asn Pro Ala Val Ser Leu Ala Met Cys Leu Phe Gly Arg Met Lys Trp  
 85 90 95

ttc aaa ttg cca ttt tat gtg gga gcc cag ttc ttg gga gcc ttt gtg 573  
 Phe Lys Leu Pro Phe Tyr Val Gly Ala Gln Phe Leu Gly Ala Phe Val  
 100 105 110 115  
 ggg gct gca acc gtc ttt ggc att tac tat gat gga ctt atg tcc ttt 621  
 Gly Ala Ala Thr Val Phe Gly Ile Tyr Tyr Asp Gly Leu Met Ser Phe  
 120 125 130  
 gct ggt gga aaa ctg ctg atc gtg gga gaa aat gca aca gca cac att 669  
 Ala Gly Gly Lys Leu Leu Ile Val Gly Glu Asn Ala Thr Ala His Ile  
 135 140 145  
 ttt gca aca tac cca gct ccg tat cta tct ctg gcg aac gca ttt gca 717  
 Phe Ala Thr Tyr Pro Ala Pro Tyr Leu Ser Leu Ala Asn Ala Phe Ala  
 150 155 160  
 gat caa gtg gtg gcc acc atg ata ctc ctc ata atc gtc ttt gcc att 765  
 Asp Gln Val Val Ala Thr Met Ile Leu Leu Ile Ile Val Phe Ala Ile  
 165 170 175  
 ttt gac tcc aga aac ttg gga gcc ccc aga ggc cta gag ccc att gcc 813  
 Phe Asp Ser Arg Asn Leu Gly Ala Pro Arg Gly Leu Glu Pro Ile Ala  
 180 185 190 195  
 atc ggc ctc ctg att att gtc att gct tcc tcc ctg gga ctg aac agt 861  
 Ile Gly Leu Leu Ile Ile Val Ile Ala Ser Ser Leu Gly Leu Asn Ser  
 200 205 210  
 ggc tgt gcc atg aac cca gct cga gac ctg agt ccc aga ctt ttc act 909  
 Gly Cys Ala Met Asn Pro Ala Arg Asp Leu Ser Pro Arg Leu Phe Thr  
 215 220 225  
 gcc ttg gca ggc tgg ggg ttt gaa gtc ttc aga gct gga aac aac ttc 957  
 Ala Leu Ala Gly Trp Gly Phe Glu Val Phe Arg Ala Gly Asn Asn Phe  
 230 235 240  
 tgg tgg att cct gta gtg ggc cct ttg gtt ggt gct gtc att gga ggc 1005  
 Trp Trp Ile Pro Val Val Gly Pro Leu Val Gly Ala Val Ile Gly Gly  
 245 250 255  
 ctc atc tat gtt ctt gtc att gaa atc cac cat cca gag cct gac tca 1053  
 Leu Ile Tyr Val Leu Val Ile Glu Ile His His Pro Glu Pro Asp Ser  
 260 265 270 275  
 gtc ttt aag gca gaa caa tct gag gac aaa cca gag aaa tat gaa ctc 1101  
 Val Phe Lys Ala Glu Gln Ser Glu Asp Lys Pro Glu Lys Tyr Glu Leu  
 280 285 290  
 agt gtc atc atg tag tggcatgctc agctctggat ttgcagtcag tttgggattc 1156  
 Ser Val Ile Met \*  
 295  
 tcttcagaaa gatggcatct aagtgtctgt gttctttaa gctgaggtg gaatocaccc 1216  
 agttttgtct gctagccata tgggacatct aattggaaaa gcatctgcat aaaagtttgg 1276  
 aaacaatgac cacttctcta ccattgtccc ccacccacc cccagaata acgctgactg 1336  
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 aggtaagcac taataactcg gcatcttgac gatagtccca tttgggtggt ttcagctgca 1456  
 ctatctgtat gaaatggtgt caccaaaacc cttttcttca gtatcgacaa agattacatt 1516  
 ctgagtacca accaaaccct aaattgaaag acaaaactat ggtttcagtc aacatattca 1576  
 tgaattaggg agctaattggg ttaagcttcc agttcccgtc atgctactgg atttgtataa 1636

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atactgatat tctccaaacc tagtgggtga gggagcaaga gaatgcagct ggaaggcaca 1696
agggggaggac attgtggcat tcagaaactg caggagacaa gatgaatttg agaagccaaa 1756
tggaattttt aatggaaacc atttatcaga ttaatctctt gctctcctgc attttagagg 1816
acaccaatta atttcctggg ctttagtata taataaccta aaataccatt gtaacctcag 1876
tcatgaaaaa tacatcactc tgtcttttta gctcaaagt attttcctaa ttgcccactt 1936
gagaacagac atttgacaag ttatatcaac gactgtgctt gtccattatt ttacacatgc 1996
cctagaagcc aaaactgaaa gccactggat cctgggtctag ctgaatcttc agagtgggag 2056
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gacaaaatgt tcctcaatct taagatacaa agaccctcat tgtctgggtc tattcccaca 2416
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gcttcctgcc agcaccaaac attacattca ggggatttcc tctggctcag tcttttcccc 2596
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caaaaggcatt aggtttccca actgctttgt gctgatatca gaacagcaga aattaaatgt 2776
gaaatgtttc tgatgactta tgttctacaa tctatggaca tacgggattt tttttctttg 2836
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<210> 46

<211> 295

<212> PRT

<213> Homo sapiens

<400> 46

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Val Leu Lys Ser Ser Leu Ala Lys Glu Thr Leu Ser Glu Phe Leu Gly
      20              25              30
Thr Phe Ile Leu Ile Val Leu Gly Cys Gly Cys Val Ala Gln Ala Ile
      35              40              45
Leu Ser Arg Gly Arg Phe Gly Gly Val Ile Thr Ile Asn Val Gly Phe
      50              55              60
Ser Met Ala Val Ala Met Ala Ile Tyr Val Ala Gly Gly Val Ser Gly
      65              70              75              80
Gly His Ile Asn Pro Ala Val Ser Leu Ala Met Cys Leu Phe Gly Arg
      85              90              95
Met Lys Trp Phe Lys Leu Pro Phe Tyr Val Gly Ala Gln Phe Leu Gly
      100             105             110
Ala Phe Val Gly Ala Ala Thr Val Phe Gly Ile Tyr Tyr Asp Gly Leu
      115             120             125
Met Ser Phe Ala Gly Gly Lys Leu Leu Ile Val Gly Glu Asn Ala Thr
      130             135             140
Ala His Ile Phe Ala Thr Tyr Pro Ala Pro Tyr Leu Ser Leu Ala Asn
      145             150             155             160
Ala Phe Ala Asp Gln Val Val Ala Thr Met Ile Leu Leu Ile Ile Val
      165             170             175
Phe Ala Ile Phe Asp Ser Arg Asn Leu Gly Ala Pro Arg Gly Leu Glu
      180             185             190
Pro Ile Ala Ile Gly Leu Leu Ile Ile Val Ile Ala Ser Ser Leu Gly
      195             200             205
Leu Asn Ser Gly Cys Ala Met Asn Pro Ala Arg Asp Leu Ser Pro Arg
      210             215             220
Leu Phe Thr Ala Leu Ala Gly Trp Gly Phe Glu Val Phe Arg Ala Gly
      225             230             235             240
Asn Asn Phe Trp Trp Ile Pro Val Val Gly Pro Leu Val Gly Ala Val
      245             250             255
Ile Gly Gly Leu Ile Tyr Val Leu Val Ile Glu Ile His His Pro Glu

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      260      265      270
Pro Asp Ser Val Phe Lys Ala Glu Gln Ser Glu Asp Lys Pro Glu Lys
      275      280      285
Tyr Glu Leu Ser Val Ile Met
      290      295

<210> 47
<211> 1869
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1869)

<400> 47
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Met Arg Leu Leu Arg Arg Arg His Met Pro Leu Arg Leu Ala Met Val
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ggc tgc gcc ttt gtg ctc ttc ctc ttc ctc ctg cat agg gat gtg agc 96
Gly Cys Ala Phe Val Leu Phe Leu Phe Leu Leu His Arg Asp Val Ser
             20             25             30

agc aga gag gag gcc aca gag aag ccg tgg ctg aag tcc ctg gtg agc 144
Ser Arg Glu Glu Ala Thr Glu Lys Pro Trp Leu Lys Ser Leu Val Ser
             35             40             45

cgg aag gat cac gtc ctg gac ctc atg ctg gag gcc atg aac aac ctt 192
Arg Lys Asp His Val Leu Asp Leu Met Leu Glu Ala Met Asn Asn Leu
             50             55             60

aga gat tca atg ccc aag ctc caa atc agg gct cca gaa gcc cag cag 240
Arg Asp Ser Met Pro Lys Leu Gln Ile Arg Ala Pro Glu Ala Gln Gln
             65             70             75             80

act ctg ttc tcc ata aac cag tcc tgc ctc cct ggg ttc tat acc cca 288
Thr Leu Phe Ser Ile Asn Gln Ser Cys Leu Pro Gly Phe Tyr Thr Pro
             85             90             95

gct gaa ctg aag ccc ttc tgg gaa cgg cca cca cag gac ccc aat gcc 336
Ala Glu Leu Lys Pro Phe Trp Glu Arg Pro Pro Gln Asp Pro Asn Ala
             100             105             110

cct ggg gca gat gga aaa gca ttt cag aag agc aag tgg acc ccc ctg 384
Pro Gly Ala Asp Gly Lys Ala Phe Gln Lys Ser Lys Trp Thr Pro Leu
             115             120             125

gag acc cag gaa aag gaa gaa ggc tat aag aag cac tgt ttc aat gcc 432
Glu Thr Gln Glu Lys Glu Glu Gly Tyr Lys Lys His Cys Phe Asn Ala
             130             135             140

ttt gcc agc gac cgg atc tcc ctg cag agg tcc ctg ggg cca gac acc 480
Phe Ala Ser Asp Arg Ile Ser Leu Gln Arg Ser Leu Gly Pro Asp Thr
             145             150             155             160

cga cca cct gag tgt gtg gac cag aag ttc cgg cgc tgc ccc cca ctg 528
Arg Pro Pro Glu Cys Val Asp Gln Lys Phe Arg Arg Cys Pro Pro Leu
             165             170             175

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gcc acc acc agc gtg atc att gtg ttc cac aac gaa gcc tgg tcc aca	576
Ala Thr Thr Ser Val Ile Ile Val Phe His Asn Glu Ala Trp Ser Thr	
180 185 190	
ctg ctg cga aca gtg tac agc gtc cta cac acc acc cct gcc atc ttg	624
Leu Leu Arg Thr Val Tyr Ser Val Leu His Thr Thr Pro Ala Ile Leu	
195 200 205	
ctc aag gag atc ata ctg gtg gat gat gcc agc aca gag gag cac cta	672
Leu Lys Glu Ile Ile Leu Val Asp Asp Ala Ser Thr Glu Glu His Leu	
210 215 220	
aag gag aag ctg gag cag tac gtg aag cag ctg cag gtg gtg agg gtg	720
Lys Glu Lys Leu Glu Gln Tyr Val Lys Gln Leu Gln Val Val Arg Val	
225 230 235 240	
gtg cgg cag gag gag cgg aag ggg ttg atc acc gcc cgg ctg ctg ggg	768
Val Arg Gln Glu Glu Arg Lys Gly Leu Ile Thr Ala Arg Leu Leu Gly	
245 250 255	
gcc agc gtg gca cag ggc gag gtg ctc acg ttc ctg gat gcc cac tgt	816
Ala Ser Val Ala Gln Ala Glu Val Leu Thr Phe Leu Asp Ala His Cys	
260 265 270	
gag tgc ttc cac ggc tgg ctg gag ccc ctc ctg gct cga atc gct gag	864
Glu Cys Phe His Gly Trp Leu Glu Pro Leu Leu Ala Arg Ile Ala Glu	
275 280 285	
gac aag aca gtg gtg gtg agc cca gac atc gtc acc atc gac ctt aat	912
Asp Lys Thr Val Val Val Ser Pro Asp Ile Val Thr Ile Asp Leu Asn	
290 295 300	
act ttt gag ttc gcc aag ccc gtc cag agg ggc aga gtc cat agc cga	960
Thr Phe Glu Phe Ala Lys Pro Val Gln Arg Gly Arg Val His Ser Arg	
305 310 315 320	
ggc aac ttt gac tgg agc ctg acc ttc ggc tgg gaa aca ctt cct cca	1008
Gly Asn Phe Asp Trp Ser Leu Thr Phe Gly Trp Glu Thr Leu Pro Pro	
325 330 335	
cat gag aag cag agg cgc aag gat gaa aca tac ccc atc aaa tcc ccg	1056
His Glu Lys Gln Arg Arg Lys Asp Glu Thr Tyr Pro Ile Lys Ser Pro	
340 345 350	
acg ttt gct ggt ggc ctc ttc tcc atc ccc aag tcc tac ttt gag cac	1104
Thr Phe Ala Gly Gly Leu Phe Ser Ile Pro Lys Ser Tyr Phe Glu His	
355 360 365	
atc ggt acc tat gat aat cag atg gag atc tgg gga ggg gag aac gtg	1152
Ile Gly Thr Tyr Asp Asn Gln Met Glu Ile Trp Gly Gly Glu Asn Val	
370 375 380	
gaa atg tcc ttc cgg gtg tgg cag tgt ggg ggc cag ctg gag atc atc	1200
Glu Met Ser Phe Arg Val Trp Gln Cys Gly Gly Gln Leu Glu Ile Ile	
385 390 395 400	
ccc tgc tct gtc gta ggc cat gtg ttc cgg acc aag agc ccc cac acc	1248
Pro Cys Ser Val Val Gly His Val Phe Arg Thr Lys Ser Pro His Thr	
405 410 415	
ttc ccc aag ggc act agt gtc att gct cgc aat caa gtg cgc ctg gca	1296

Phe Pro Lys Gly Thr Ser Val Ile Ala Arg Asn Gln Val Arg Leu Ala  
 420 425 430  
 gag gtc tgg atg gac agc tac aag aag att ttc tat agg aga aat ctg 1344  
 Glu Val Trp Met Asp Ser Tyr Lys Lys Ile Phe Tyr Arg Arg Asn Leu  
 435 440 445  
 cag gca gca aag atg gcc caa gag aaa tcc ttc ggt gac att tcg gaa 1392  
 Gln Ala Ala Lys Met Ala Gln Glu Lys Ser Phe Gly Asp Ile Ser Glu  
 450 455 460  
 cga ctg cag ctg agg gaa caa ctg cac tgt cac aac ttt tcc tgg tac 1440  
 Arg Leu Gln Leu Arg Glu Gln Leu His Cys His Asn Phe Ser Trp Tyr  
 465 470 475 480  
 ctg cac aat gtc tac cca gag atg ttt gtt cct gac ctg acg ccc acc 1488  
 Leu His Asn Val Tyr Pro Glu Met Phe Val Pro Asp Leu Thr Pro Thr  
 485 490 495  
 ttc tat ggt gcc atc aag aac ctc ggc acc aac caa tgc ctg gat gtg 1536  
 Phe Tyr Gly Ala Ile Lys Asn Leu Gly Thr Asn Gln Cys Leu Asp Val  
 500 505 510  
 ggt gag aac aac cgc ggg ggg aag ccc ctc atc atg tac tcc tgc cac 1584  
 Gly Glu Asn Asn Arg Gly Gly Lys Pro Leu Ile Met Tyr Ser Cys His  
 515 520 525  
 ggc ctt ggc ggc aac cag tac ttt gag tac aca act cag agg gac ctt 1632  
 Gly Leu Gly Gly Asn Gln Tyr Phe Glu Tyr Thr Thr Gln Arg Asp Leu  
 530 535 540  
 cgc cac aac atc gca aag cag ctg tgt cta cat gtc agc aag ggt gct 1680  
 Arg His Asn Ile Ala Lys Gln Leu Cys Leu His Val Ser Lys Gly Ala  
 545 550 555 560  
 ctg ggc ctt ggg agc tgt cac ttc act ggc aag aat agc cag gtc ccc 1728  
 Leu Gly Leu Gly Ser Cys His Phe Thr Gly Lys Asn Ser Gln Val Pro  
 565 570 575  
 aag gac gag gaa tgg gaa ttg gcc cag gat cag ctc atc agg aac tca 1776  
 Lys Asp Glu Glu Trp Glu Leu Ala Gln Asp Gln Leu Ile Arg Asn Ser  
 580 585 590  
 gga tct ggt acc tgc ctg aca tcc cag gac aaa aag cca gcc atg gcc 1824  
 Gly Ser Gly Thr Cys Leu Thr Ser Gln Asp Lys Lys Pro Ala Met Ala  
 595 600 605  
 ccc tgc aat ccc agt gac ccc cat cag ttg tgg ctc ttt gtc tag 1869  
 Pro Cys Asn Pro Ser Asp Pro His Gln Leu Trp Leu Phe Val \*  
 610 615 620

&lt;210&gt; 48

&lt;211&gt; 622

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 48

Met Arg Leu Leu Arg Arg Arg His Met Pro Leu Arg Leu Ala Met Val  
 1 5 10 15

Gly Cys Ala Phe Val Leu Phe Leu Phe Leu Leu His Arg Asp Val Ser  
 20 25 30  
 Ser Arg Glu Glu Ala Thr Glu Lys Pro Trp Leu Lys Ser Leu Val Ser  
 35 40 45  
 Arg Lys Asp His Val Leu Asp Leu Met Leu Glu Ala Met Asn Asn Leu  
 50 55 60  
 Arg Asp Ser Met Pro Lys Leu Gln Ile Arg Ala Pro Glu Ala Gln Gln  
 65 70 75 80  
 Thr Leu Phe Ser Ile Asn Gln Ser Cys Leu Pro Gly Phe Tyr Thr Pro  
 85 90 95  
 Ala Glu Leu Lys Pro Phe Trp Glu Arg Pro Pro Gln Asp Pro Asn Ala  
 100 105 110  
 Pro Gly Ala Asp Gly Lys Ala Phe Gln Lys Ser Lys Trp Thr Pro Leu  
 115 120 125  
 Glu Thr Gln Glu Lys Glu Glu Gly Tyr Lys Lys His Cys Phe Asn Ala  
 130 135 140  
 Phe Ala Ser Asp Arg Ile Ser Leu Gln Arg Ser Leu Gly Pro Asp Thr  
 145 150 155 160  
 Arg Pro Pro Glu Cys Val Asp Gln Lys Phe Arg Arg Cys Pro Pro Leu  
 165 170 175  
 Ala Thr Thr Ser Val Ile Ile Val Phe His Asn Glu Ala Trp Ser Thr  
 180 185 190  
 Leu Leu Arg Thr Val Tyr Ser Val Leu His Thr Thr Pro Ala Ile Leu  
 195 200 205  
 Leu Lys Glu Ile Ile Leu Val Asp Asp Ala Ser Thr Glu Glu His Leu  
 210 215 220  
 Lys Glu Lys Leu Glu Gln Tyr Val Lys Gln Leu Gln Val Val Arg Val  
 225 230 235 240  
 Val Arg Gln Glu Glu Arg Lys Gly Leu Ile Thr Ala Arg Leu Leu Gly  
 245 250 255  
 Ala Ser Val Ala Gln Ala Glu Val Leu Thr Phe Leu Asp Ala His Cys  
 260 265 270  
 Glu Cys Phe His Gly Trp Leu Glu Pro Leu Leu Ala Arg Ile Ala Glu  
 275 280 285  
 Asp Lys Thr Val Val Val Ser Pro Asp Ile Val Thr Ile Asp Leu Asn  
 290 295 300  
 Thr Phe Glu Phe Ala Lys Pro Val Gln Arg Gly Arg Val His Ser Arg  
 305 310 315 320  
 Gly Asn Phe Asp Trp Ser Leu Thr Phe Gly Trp Glu Thr Leu Pro Pro  
 325 330 335  
 His Glu Lys Gln Arg Arg Lys Asp Glu Thr Tyr Pro Ile Lys Ser Pro  
 340 345 350  
 Thr Phe Ala Gly Gly Leu Phe Ser Ile Pro Lys Ser Tyr Phe Glu His  
 355 360 365  
 Ile Gly Thr Tyr Asp Asn Gln Met Glu Ile Trp Gly Gly Glu Asn Val  
 370 375 380  
 Glu Met Ser Phe Arg Val Trp Gln Cys Gly Gly Gln Leu Glu Ile Ile  
 385 390 395 400  
 Pro Cys Ser Val Val Gly His Val Phe Arg Thr Lys Ser Pro His Thr  
 405 410 415  
 Phe Pro Lys Gly Thr Ser Val Ile Ala Arg Asn Gln Val Arg Leu Ala  
 420 425 430  
 Glu Val Trp Met Asp Ser Tyr Lys Lys Ile Phe Tyr Arg Arg Asn Leu  
 435 440 445  
 Gln Ala Ala Lys Met Ala Gln Glu Lys Ser Phe Gly Asp Ile Ser Glu  
 450 455 460  
 Arg Leu Gln Leu Arg Glu Gln Leu His Cys His Asn Phe Ser Trp Tyr  
 465 470 475 480  
 Leu His Asn Val Tyr Pro Glu Met Phe Val Pro Asp Leu Thr Pro Thr  
 485 490 495  
 Phe Tyr Gly Ala Ile Lys Asn Leu Gly Thr Asn Gln Cys Leu Asp Val

	500		505		510										
Gly	Glu	Asn	Asn	Arg	Gly	Gly	Lys	Pro	Leu	Ile	Met	Tyr	Ser	Cys	His
	515						520					525			
Gly	Leu	Gly	Gly	Asn	Gln	Tyr	Phe	Glu	Tyr	Thr	Thr	Gln	Arg	Asp	Leu
	530						535					540			
Arg	His	Asn	Ile	Ala	Lys	Gln	Leu	Cys	Leu	His	Val	Ser	Lys	Gly	Ala
	545				550					555					560
Leu	Gly	Leu	Gly	Ser	Cys	His	Phe	Thr	Gly	Lys	Asn	Ser	Gln	Val	Pro
			565						570					575	
Lys	Asp	Glu	Glu	Trp	Glu	Leu	Ala	Gln	Asp	Gln	Leu	Ile	Arg	Asn	Ser
			580						585					590	
Gly	Ser	Gly	Thr	Cys	Leu	Thr	Ser	Gln	Asp	Lys	Lys	Pro	Ala	Met	Ala
	595						600					605			
Pro	Cys	Asn	Pro	Ser	Asp	Pro	His	Gln	Leu	Trp	Leu	Phe	Val		
	610					615					620				

<210> 49  
 <211> 1544  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (87)...(1517)

<400> 49  
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 aagagtggaa gcgaggaagg aacagg atg att aga cct cag ctg cgg acc gcg 113  
 Met Ile Arg Pro Gln Leu Arg Thr Ala  
 1 5

ggg ctg gga cga tgc ctc ctg ccg ggg ctg ctg ctg ctc ctg gtg ccc 161  
 Gly Leu Gly Arg Cys Leu Leu Pro Gly Leu Leu Leu Leu Val Pro  
 10 15 20 25

gtc ctc tgg gcc ggg gct gaa aag cta cat acc cag ccc tcc tgc ccc 209  
 Val Leu Trp Ala Gly Ala Glu Lys Leu His Thr Gln Pro Ser Cys Pro  
 30 35 40

gcg gtc tgc cag ccc acg cgc tgc ccc gcg ctg ccc acc tgc gcg ctg 257  
 Ala Val Cys Gln Pro Thr Arg Cys Pro Ala Leu Pro Thr Cys Ala Leu  
 45 50 55

ggg acc acg ccg gtg ttc gac ctg tgc cgc tgt tgc cgc gtc tgc ccc 305  
 Gly Thr Thr Pro Val Phe Asp Leu Cys Arg Cys Cys Arg Val Cys Pro  
 60 65 70

gcg gcc gag cgt gaa gtc tgc ggc ggg gcg cag ggc caa ccg tgc gcc 353  
 Ala Ala Glu Arg Glu Val Cys Gly Gly Ala Gln Gly Gln Pro Cys Ala  
 75 80 85

ccg ggg ctg cag tgc ctc cag ccg ctg cgc ccc ggg ttc ccc agc acc 401  
 Pro Gly Leu Gln Cys Leu Gln Pro Leu Arg Pro Gly Phe Pro Ser Thr  
 90 95 100 105

tgc ggt tgc ccg acg ctg gga ggg gcc gtg tgc ggc agc gac agg cgc 449  
 Cys Gly Cys Pro Thr Leu Gly Gly Ala Val Cys Gly Ser Asp Arg Arg  
 110 115 120

acc tac ccc agc atg tgc gcg ctc ccg gcc gaa aac cgc gcc gcg cgc 497

Thr Tyr Pro Ser Met Cys Ala Leu Arg Ala Glu Asn Arg Ala Ala Arg	125	130	135	
cgc ctg ggc aag gtc ccg gcc gtg cct gtg cag tgg ggg aac tgc ggg	545			
Arg Leu Gly Lys Val Pro Ala Val Pro Val Gln Trp Gly Asn Cys Gly	140	145	150	
gat aca ggc acc aga agc gca gcc ccg ctc agg agg aat tac aac ttc	593			
Asp Thr Gly Thr Arg Ser Ala Gly Pro Leu Arg Arg Asn Tyr Asn Phe	155	160	165	
atc gcc gcg gtg gtg gag aag gtg gcg cca tcg gtg gtt cac gtg cag	641			
Ile Ala Ala Val Val Glu Lys Val Ala Pro Ser Val Val His Val Gln	170	175	180	185
ctg tgg ggc agg tta ctt cac gcc agc agg ctt gtt cct gtg tac agt	689			
Leu Trp Gly Arg Leu Leu His Gly Ser Arg Leu Val Pro Val Tyr Ser	190	195	200	
ggc tct ggg ttc ata gtg tct gag gac ggg ctc att att acc aat gcc	737			
Gly Ser Gly Phe Ile Val Ser Glu Asp Gly Leu Ile Ile Thr Asn Ala	205	210	215	
cat gtt gtc agg aac cag cag tgg att gag gtg gtg ctc cag aat ggg	785			
His Val Val Arg Asn Gln Gln Trp Ile Glu Val Val Leu Gln Asn Gly	220	225	230	
gcc cgt tat gaa gct gtt gtc aag gat att gac ctt aaa ttg gat ctt	833			
Ala Arg Tyr Glu Ala Val Val Lys Asp Ile Asp Leu Lys Leu Asp Leu	235	240	245	
gcg gtg att aag att gaa tca aat gct gaa ctt cct gta ctg atg ctg	881			
Ala Val Ile Lys Ile Glu Ser Asn Ala Glu Leu Pro Val Leu Met Leu	250	255	260	265
gga aga tca tct gac ctt ccg gct gga gag ttt gtg gtg gct ttg ggc	929			
Gly Arg Ser Ser Leu Arg Ala Gly Glu Phe Val Val Ala Leu Gly	270	275	280	
agc cca ttt tct ctg cag aac aca gct act gca gga att gtc agc acc	977			
Ser Pro Phe Ser Leu Gln Asn Thr Ala Thr Ala Gly Ile Val Ser Thr	285	290	295	
aaa cag cga ggg ggc aaa gaa ctg ggg atg aag gat tca gat atg gac	1025			
Lys Gln Arg Gly Gly Lys Glu Leu Gly Met Lys Asp Ser Asp Met Asp	300	305	310	
tac gtc cag att gat gcc aca att aac tat ggg aat tct ggt ggt cct	1073			
Tyr Val Gln Ile Asp Ala Thr Ile Asn Tyr Gly Asn Ser Gly Gly Pro	315	320	325	
ctg gtg aac ttg gat ggt gat gtg att ggc gtc aat tca ttg agg gtg	1121			
Leu Val Asn Leu Asp Gly Asp Val Ile Gly Val Asn Ser Leu Arg Val	330	335	340	345
act gat gga atc tcc ttt gca att cct tca gat cga gtt agg cag ttc	1169			
Thr Asp Gly Ile Ser Phe Ala Ile Pro Ser Asp Arg Val Arg Gln Phe	350	355	360	
ttg gca gaa tac cat gag cac cag atg aaa gga aag gcg ttt tca aat	1217			
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(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
23 September 2004 (23.09.2004)

PCT

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**WO 2004/080535 A3**

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(22) International Filing Date: 27 February 2004 (27.02.2004)

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(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

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(71) Applicant (for all designated States except US): MILLENNIUM PHARMACEUTICALS, INC. [US/US]; 40 Landsdowne Street, Cambridge, MA 02139 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): POWELL, Douglas, M. [US/US]; 62 Grist Mill Road, Littleton, MA 01460 (US).

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(74) Agent: SIOUSSAT, Tracy, M.; Millennium Pharmaceuticals, INC., 40 Landsdowne Street, Cambridge, MA 02139 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS AND COMPOSITIONS FOR TREATING AIDS AND HIV-RELATED DISORDERS USING 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982, OR 46777

(57) Abstract: The present invention relates to methods for the diagnosis and treatment of AIDS or an HIV-related disorder or disorders. Specifically, the present invention identifies the differential expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982, and 46777 genes in tissues relating to AIDS or an HIV-related disorder, relative to their expression in normal, or non-AIDS or HIV-related disease states, and/or in response to manipulations relevant to AIDS or an HIV-related disorder. The present invention describes methods for the diagnostic evaluation and prognosis of various HIV-related disorders, and for the identification of subjects exhibiting a predisposition to such conditions. The invention also provides methods for identifying a compound capable of modulating AIDS or an HIV-related disorder or disorders. The present invention also provides methods for the identification and therapeutic use of compounds as treatments of AIDS or an HIV-related disorder.

WO 2004/080535 A3

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/06120

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/70; G01N 33/53

US CL : 435/5, 7.1, 7.71

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/5, 7.1, 7.71

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
USPATFUL, WPIDS, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2002/0052032 A1 (MEYERS, R., et al.) 02 May 2002 (02.05.2002), see entire document.	1-20
A	US 2002/0042371 A1 (MEYERS, R., et al.) 11 April 2002 (11.04.2002), see entire document.	1-20

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

13 September 2004 (13.09.2004)

Date of mailing of the international search report

05 OCT 2004

Name and mailing address of the ISA/US


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Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

JS Parkin


Telephone No. (703) 308-1111



### Abstract

**Background:**  
 Sustiva (Efavirenz) Oral Solution is approved for children  $\geq 3$  years of age in Europe only. Efavirenz capsule contents mixed with food vehicles will be one of the modes of administration in pediatric study, AI266922, which will be conducted to gain approval of oral solution in children  $< 3$  years of age worldwide.


**Methods:**  
 Open-label, three-period, three-treatment cross over study with two treatment groups in twenty-four healthy subjects (12 subjects / treatment group). Treatment Group 1 received treatments A (3 x 200 mg EFV intact capsule fasted), B (EFV capsule contents + applesauce) and C (EFV capsule contents + grape jelly). Treatment Group 2 will receive treatments A, D (EFV capsule contents + yogurt), and E (EFV capsule contents + baby formula).



### Abstract


**Results:**  
 All comparisons of Treatments B and C to Reference Treatment A met the criteria for bioequivalence with respect to AUC(INF) and AUC(0-T). Although C<sub>max</sub> did not meet the criteria for bioequivalence, mean C<sub>max</sub> for Treatments B and C were within 7% of the mean C<sub>max</sub> for Reference Treatment A. Treatment E was bioequivalent to Reference Treatment A with respect to C<sub>max</sub>, AUC(INF), and AUC(0-T). With respect to AUC(INF) and AUC(0-T), the bioavailability of treatment D was bioequivalent to Reference Treatment A. Mean C<sub>max</sub> for Treatment D was approximately 17% higher compared to Reference Treatment A and did not meet bioequivalence criteria.

**Conclusions:**  
 The AUC of efavirenz from capsule contents mixed and administered with each of the food vehicles (applesauce, grape jelly, yogurt) or baby formula, was bioequivalent to the AUC of the intact capsule formulation administered under fasted conditions. Efavirenz can be administered with applesauce, grape jelly, yogurt, or baby formula. Grape jelly was the most palatable food vehicle used to administer efavirenz capsule contents.



### Background

- Non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for the treatment of HIV-1 infection in combination with other medications
- Capsule approved for children  $\geq 3$  years of age
- Oral Solution approved for children  $\geq 3$  years of age in Europe only
- Pediatric study AI266922: To gain approval of oral solution in children  $< 3$  years of age worldwide
  - EFV capsule contents mixed with food vehicles will be one of the modes of administration
- Recommended by the FDA as a prerequisite to the EFV pediatric trial
  - Relative bioavailability of the new formulation compared to the adult formulation (US FDA DRAFT Guidance on General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products; Nov 10, 1998)

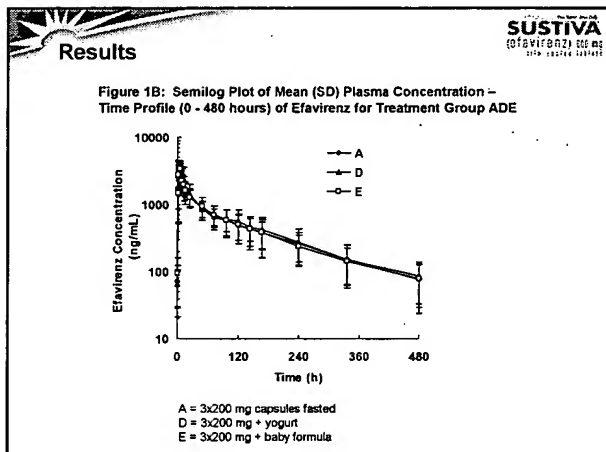
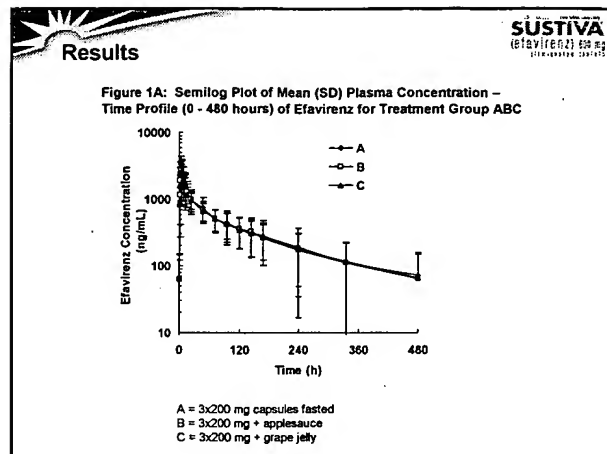
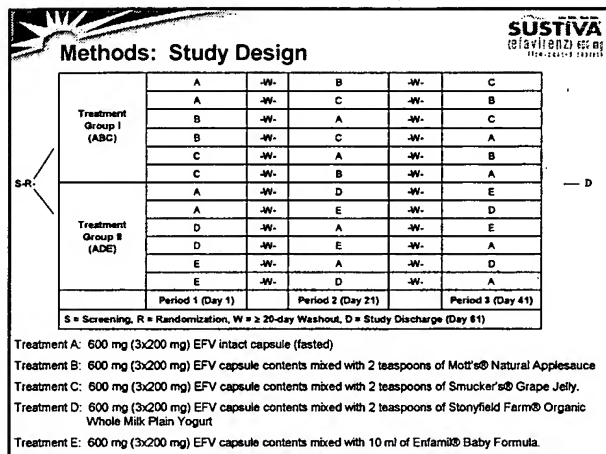


### Objectives

- **Primary Objective:** To assess the bioavailability of efavirenz capsule contents when mixed with one of three food vehicles (applesauce, grape jelly, or yogurt) or baby formula, relative to the intact capsule formulation administered under fasted conditions.
- **Secondary Objective:** To assess the safety of efavirenz.

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**Results**

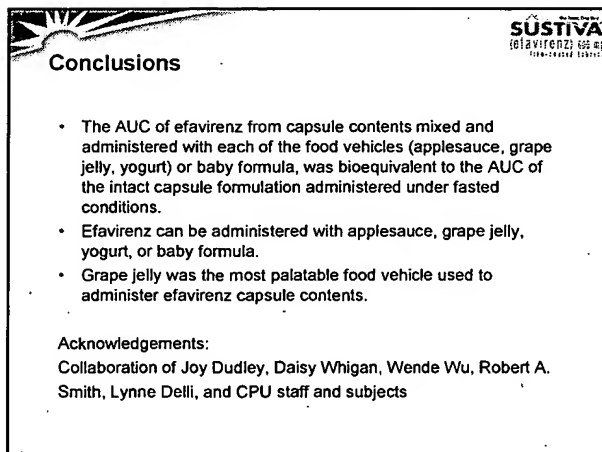
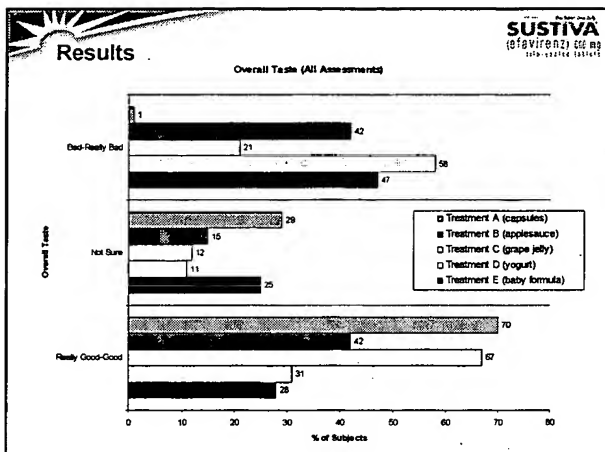
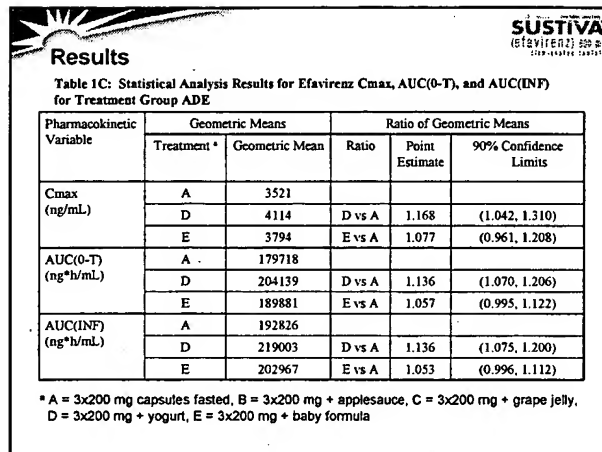
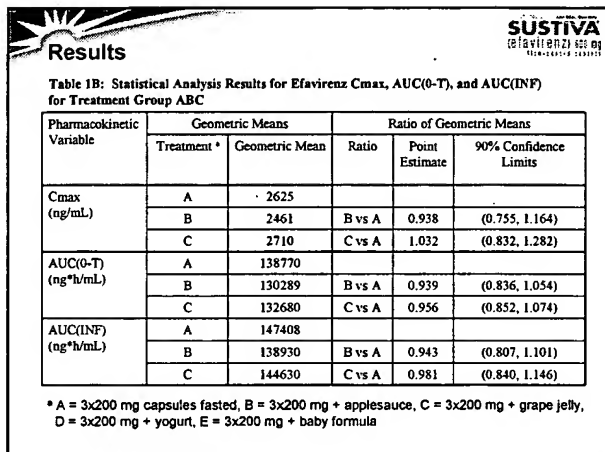
**SUSTIVA**  
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TABLETS

Table 1A: Summary Statistics for Efavirenz Pharmacokinetic Parameters by Group and Treatment

Group	Treatment *	Efavirenz Pharmacokinetic Parameters				
		C <sub>max</sub> (ng/mL) Geom. Mean (CV %)	AUC(0-T) (ng.h/mL) Geom. Mean (CV %)	AUC(0-∞) (ng.h/mL) Geom. Mean (CV %)	T <sub>max</sub> (h) Median (min, max)	T-1/2 (h) Mean (SD)
ABC (n = 10)	A	2693 (48%)	153067 (55%)	142788 (45%)	4.5 (2.0, 8.0)	117 (53)
	B	2475 (63%)	143269 (61%)	133213 (48%)	4.0 (2.0, 8.0)	125 (69)
	C	2772 (37%)	150170 (71%)	136038 (46%)	3.0 (1.0, 5.0)	149 (139)
ADE (n = 12)	A	3522 (29%)	192825 (39%)	179718 (36%)	3.0 (2.0, 4.0)	122 (40)
	D	4114 (27%)	219003 (32%)	204139 (29%)	4.0 (1.0, 12.0)	127 (41)
	E	3794 (23%)	202967 (33%)	189881 (30%)	4.0 (1.0, 12.0)	127 (39)

\* A = 3x200 mg capsules fasted, B = 3x200 mg + applesauce, C = 3x200 mg + grape jelly, D = 3x200 mg + yogurt, E = 3x200 mg + baby formula

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